METHODS OF TREATING HAIR LOSS COMPRISING ADMINISTERING INDOLINE COMPOUND

FIELD OF THE INVENTION

The present invention relates to methods for treating hair loss in mammals, including arresting hair loss, reversing hair loss and / or promoting hair growth. The methods comprise administering a composition wherein the composition comprises an indoline compound.

BACKGROUND OF THE INVENTION

Hair loss is a common problem which occurs, for example, through natural processes or is often chemically promoted through the use of certain therapeutic drugs designed to alleviate conditions such as cancer. Often such hair loss is accompanied by lack of hair regrowth which causes partial or full baldness. Such baldness is cosmetically unappealing, and is particularly distressing to the person experiencing the hair loss.

As is well-known in the art, hair growth occurs by a cycle of activity which involves alternating periods of growth and rest. This cycle is often divided into three main stages which are known as anagen, catagen, and telogen. Anagen is the growth phase of the cycle and may be characterized by penetration of the hair follicle deep into the dermis with rapid proliferation of cells which are differentiating to form hair. The next phase is catagen, which is a transitional stage marked by the cessation of cell division, and during which the hair follicle regresses through the dermis and hair growth is ceased. The next phase, telogen, is often characterized as the resting stage during which the regressed follicle contains a germ with tightly packed dermal papilla cells. At telogen, the initiation of a new anagen phase is caused by rapid cell proliferation in the germ, expansion of the dermal papilla, and elaboration of basement membrane components. This cycle is repeated throughout hair growth. Wherein hair growth ceases, most of the hair follicles reside in telogen and anagen is not engaged, thus causing the onset of full or partial baldness.

There have been many attempts in the literature to invoke the regrowth of hair by, for example, the promotion or prolongation of anagen. Currently, there are two drugs approved by the United States Food and Drug Administration for the treatment of male pattern baldness: topical minoxidil (6-(1-piperidinyl)-2,4-pyrimidine-3-oxide, marketed as Rogaine® by Pharmacia & Upjohn), and oral finasteride (marketed as Propecia® by Merck & Co., Inc.).

There are conflicting reports, however, regarding the ability of minoxidil to grow hair. In fact, early clinical studies investigating decreased blood pressure *via* the use of minoxidil did not even mention hypertrichosis (hair growth) as a side effect. See Dormois et al., "Minoxidil in Severe Hypertension: Value When Conventional Drugs Have Failed", American Heart Journal, Vol. 90, pp. 360 - 368 (1975). Indeed, the manufacturers of minoxidil have reported only limited hair growth in a portion of patients using minoxidil. See, e.g., Physician's Desk Reference®, 49th

Ed. (1995), p. 2580. Furthermore, serious side effects of minoxidil are possible, including vasodilation (which leads to retention of fluid around the heart and increased heart rate), difficulty in breathing, and weight gain. Physician's Desk Reference®, 49th Ed. (1995), p. 2581.

Furthermore, while early indicators show that Propecia® may be more effective than Rogaine®, patients using Propecia® are experiencing limited hair growth. See The New England Journal of Medicine, Vol. 338, No. 9, February 26, 1998. Furthermore, potential side effects of Propecia® are serious. Propecia® may cause impotence, decreased sexual drive, decreased volume of ejaculate, breast tenderness and enlargement, and hypersensitivity reactions, including lip swelling and skin rash. Furthermore, Propecia® is not indicated for women and children. In fact, women who are pregnant or potentially pregnant should not even handle crushed or broken tablets containing the drug. See Physician's Desk Reference®, 52th Ed. (1998), p. 1737 and The New England Journal of Medicine, Vol. 338, No. 9, February 26, 1998.

Separately, it has been reported that certain anti-inflammatories, typically in combination with another active agent, may be utilized to promote the growth of hair. See e.g., Bass, U.S. Patent No. 5,753,713, issued May 19, 1998 which discloses use of an anti-inflammatory in combination with a bactericide. However, it has also been reported that hair growth may be either promoted or prevented through use of anti-inflammatories, depending on the nature of the anti-inflammatory agent. For example, as is well-known in the art, inflammation may be associated with lipoxygenase activity and / or cyclooxygenase activity. However, Duranton et al., EP 0,648,488, assigned to L'Oreal, published April 19, 1995, reports that hair growth may be promoted through use of a lipoxygenase inhibitor and prevented through use of a cyclooxygenase inhibitor.

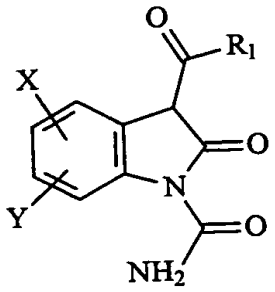
Surprisingly, the present inventor has discovered that indoline compounds, as described herein, are effective for treating hair loss in mammals, including arresting hair loss, reversing hair loss and / or promoting hair growth. See Duranton et al., EP 0,648,488, assigned to L'Oreal, published April 19, 1995. Such treatment may be either alone or in combination with one or more other agents useful for treating hair loss. Certain of these compounds will have anti-inflammatory properties as well, including cyclooxygenase inhibition, which has been heretofore described as being detrimental for treatment of hair loss. For example, the present inventor has discovered that tenidap (5-chloro-3-(2-thenoyl)-2-oxindole-1-carboxamide), which has been extensively studied for various properties including, for example, anti-inflammation and use for treatment of Alzheimer's Disease, is surprisingly useful for treating hair loss. Additionally, the present inventor has discovered that hair loss may be associated with activation of cytokines (including, for example, IL-1), tumor necrosis factors, and T-cell proliferation.

In view of the issues associated with currently utilized hair growth treatments, it is evident that there is a continuing need for compositions useful for effectively treating hair loss. The present inventor has surprisingly discovered that indoline compounds, having structures as defined

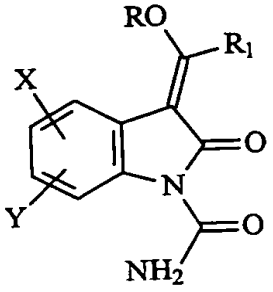
herein, are useful for treating hair loss in mammals, including arresting and / or reversing hair loss and promoting hair growth. Accordingly, the present inventor provides herein compounds, compositions, and methods of their use for effectively treating hair loss.

SUMMARY OF THE INVENTION

The present invention relates to methods for treating hair loss comprising administering a compound which have been found by the present inventor to be particularly useful for treating hair loss in mammals, including arresting and / or reversing hair loss and promoting hair growth. The compounds which may be utilized in the present method have the structure:



or



or a pharmaceutically acceptable salt, hydrate, tautomer, or biohydrolyzable amide or ester thereof, wherein X, Y, R, and R_1 are defined herein.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to methods of using compounds and compositions which are particularly useful for treating hair loss in mammals (preferably humans), including arresting and / or reversing hair loss and promoting hair growth.

Publications and patents are referred to throughout this disclosure. All references cited herein are hereby incorporated by reference.

All percentages, ratios, and proportions used herein are by weight unless otherwise specified.

Definition and Usage of Terms

The following is a list of definitions for terms used herein:

As used herein, "alkanamido" is a -NHC(O)U radical wherein U is an alkyl, alkenyl, or alkynyl, preferably an alkyl or alkenyl, and most preferably an alkyl substituent. Unless otherwise specified, alkanamidos have from 2 to about 15 carbon atoms (C_2 - C_{15}); preferably from 2 to about 10 carbon atoms (C_2 - C_{10}); more preferably from 2 to about 8 carbon atoms (C_2 - C_8), even more preferably from 2 to about 6 carbon atoms (C_2 - C_6), and most preferably from 2 to about 4 carbon atoms (C_2 - C_4).

As used herein "alkanoyl" is a -C(O)U radical wherein U is an alkyl, alkenyl, or alkynyl, preferably an alkyl or alkenyl, and most preferably an alkyl substituent. Unless otherwise specified, alkanoyls have from 2 to about 15 carbon atoms (C_2 - C_{15}); preferably from 2 to about 10 carbon atoms (C_2 - C_{10}); more preferably from 2 to about 8 carbon atoms (C_2 - C_8), even more preferably from 2 to about 6 carbon atoms (C_2 - C_6), and most preferably from 2 to about 4 carbon atoms (C_2 - C_4).

As used herein, "alkenyl" is an unsaturated hydrocarbon chain radical. Alkenyls have at least one olefinic double bond. Unless otherwise specified, alkenyls have from 2 to about 15 carbon atoms (C_2 - C_{15}); preferably from 2 to about 10 carbon atoms (C_2 - C_{10}); more preferably from 2 to about 8 carbon atoms (C_2 - C_8), and most preferably from about 2 to about 6 carbon atoms (C_2 - C_6). Non-limiting examples of alkenyls include vinyl, allyl, and butenyl.

As used herein, "alkoxy" is an oxygen radical having an alkyl, alkenyl, or alkynyl, preferably an alkyl or alkenyl, and most preferably an alkyl substituent. Unless otherwise specified, alkoxys have from 1 to about 15 carbon atoms (C_1 - C_{15}); preferably from 1 to about 10 carbon atoms (C_1 - C_{10}); more preferably from 1 to about 8 carbon atoms (C_1 - C_8), even more preferably from 1 to about 6 carbon atoms (C_1 - C_6), and most preferably from 1 to about 4 carbon atoms (C_1 - C_4). Examples of alkoxy radicals include -O-alkyl and -O-alkenyl.

As used herein, "alkoxycarbonyl" is -C(O)OK, wherein K is an alkyl. Unless otherwise specified, alkoxycarbonyls having from 2 to about 10 carbon atoms; preferably from 2 to about 8 carbon atoms, more preferably from 2 to about 5 carbon atoms, even more preferably from 2 to about 3 carbon atoms, and most preferably 2 carbon atoms.

As used herein, "alkyl" is a saturated hydrocarbon chain radical. Unless otherwise specified, alkyls have from 1 to about 15 carbon atoms (C_1 - C_{15}); preferably from 1 to about 10 carbon atoms (C_1 - C_{10}); more preferably from 1 to about 6 carbon atoms (C_1 - C_6); and most preferably from 1 to about 4 carbon atoms (C_1 - C_4). Preferred alkyls include, for example, methyl, ethyl, propyl, *iso*-propyl, and butyl.

As used herein, "alkylene" refers to an alkyl, alkenyl, or alkynyl which is a diradical. For example, "methylene" is $-CH_2-$.

As used herein, "alkylsulfonyl" is a -S(O)U or a $-S(O)_2U$ radical wherein U is an alkyl, alkenyl, or alkynyl, preferably an alkyl or alkenyl, and most preferably an alkyl substituent. Unless otherwise specified, alkylsulfonyls have from 1 to about 15 carbon atoms (C_1 - C_{15}); preferably from 1 to about 10 carbon atoms (C_1 - C_{10}); more preferably from 1 to about 8 carbon atoms (C_1 - C_8), even more preferably from 1 to about 6 carbon atoms (C_1 - C_6), and most preferably from 1 to about 4 carbon atoms (C_1 - C_4).

As used herein, "alkylthio" is a sulfur radical having an alkyl, alkenyl, or alkynyl, preferably an alkyl or alkenyl, and most preferably an alkyl substituent. Unless otherwise specified, alkylthios have from 1 to about 15 carbon atoms (C_1 - C_{15}); preferably from 1 to about

10 carbon atoms (C_1 - C_{10}); more preferably from 1 to about 8 carbon atoms (C_1 - C_8), even more preferably from 1 to about 6 carbon atoms (C_1 - C_6), and most preferably from 1 to about 4 carbon atoms (C_1 - C_4). Examples of alkoxy radicals include -S-alkyl and -S-alkenyl.

As used herein, "alkynyl" is an unsaturated hydrocarbon chain radical. Alkynyls have at least one triple bond. Unless otherwise specified, alkynyls have from 2 to about 15 carbon atoms (C_2 - C_{15}); preferably from 2 to about 10 carbon atoms (C_2 - C_{10}); more preferably from 2 to about 8 carbon atoms (C_2 - C_8), and most preferably from about 2 to about 6 carbon atoms (C_2 - C_6).

As used herein, "benzamido" is a -NHC(O)C_6C_5 radical.

As used herein, "benzoyl" is a -C(O)C_6H_5 radical.

As used herein, "biohydrolyzable amides" are amides of the compounds used in the present invention which do not interfere with the activity of the compound, or that are readily converted *in vivo* by a mammalian subject to yield an active compound.

As used herein, "biohydrolyzable esters" are esters of the compounds used in the present invention which do not interfere with the activity of the compound, or that are readily converted *in vivo* by a mammalian subject to yield an active compound.

As used herein, "carbocyclic ring", "carbocycle", or the like is a hydrocarbon ring radical. Carbocyclic rings are monocyclic or are fused, bridged, or spiro polycyclic rings. Unless otherwise specified, monocyclic rings contain from 3 to about 9 atoms, preferably from about 4 to about 7 atoms, and most preferably 5 or 6 atoms. Polycyclic rings contain from about 7 to about 17 atoms, preferably from about 7 to about 14 atoms, and most preferably 9 or 10 atoms.

As used herein, "cycloalkyl" is a saturated carbocyclic or heterocyclic ring radical. Preferably, the cycloalkyl has from 3 to 7 carbon atoms. Preferred cycloalkyl groups include, for example, cyclobutyl, cyclopentyl, and cyclohexyl.

As used herein, "cycloalkenyl" is a saturated carbocyclic or heterocyclic ring radical having at least one olefinic bond. Preferably, the cycloalkenyl has from 4 to 7 carbon atoms.

As used herein, "heteroalkenyl" is an alkenyl radical comprised of carbon atoms and one or more heteroatoms wherein the heteroatoms are selected from the group consisting of oxygen, sulfur, nitrogen, and phosphorous, more preferably, oxygen, sulfur, and nitrogen.

As used herein, "heteroalkyl" is an alkyl radical comprised of carbon atoms and one or more heteroatoms wherein the heteroatoms are selected from the group consisting of oxygen, sulfur, nitrogen, and phosphorous, more preferably, oxygen, sulfur, and nitrogen.

As used herein, "heterocyclic ring", "heterocycle", or the like is a ring radical comprised of carbon atoms and one or more heteroatoms in the ring wherein the heteroatoms are selected from the group consisting of oxygen, sulfur, nitrogen, and phosphorous, more preferably, oxygen, sulfur, and nitrogen. Heterocycles are monocyclic or are fused, bridged, or spiro polycyclic rings. Unless otherwise specified, monocycles contain from 3 to about 9 atoms, preferably from about 4 to about 7 atoms, and most preferably 5 or 6 atoms. Polycycles contain from about 7 to about 17

atoms, preferably from about 7 to about 14 atoms, and most preferably 9 or 10 atoms. Heterocyclic rings (heterocycles) may be substituted or unsubstituted.

As used herein, the term "inhibitor" with reference to lipoxygenase and / or cyclooxygenase means that the compound limits (inhibits) the enzymatic activity of one or more lipoxygenases and / or cyclooxygenases. Preferably, the indoline compound utilized herein inhibits one or more lipoxygenases and / or cyclooxygenases. Such compounds may be referred to as lipoxygenase inhibitors and cyclooxygenase inhibitors, respectively. Lipoxygenase inhibitors may be either selective or non-selective for inhibition of lipoxygenase relative to cyclooxygenase. Similarly, cyclooxygenase inhibitors may be either selective or non-selective for inhibition of cyclooxygenase relative to lipoxygenase. Preferably, the indoline compound utilized herein is a cyclooxygenase inhibitor.

As used herein, a "lower" moiety (*e.g.*, "lower" alkyl) is a moiety having 1 to about 6, preferably 1 to about 4, carbon atoms.

As used herein, "N,N-dialkylsulfamoyl" is a $-SO_2NUV$ radical wherein U and V are each, independently, alkyls having from one to four carbon atoms (C_1 - C_4).

As used herein, "pharmaceutically acceptable" means suitable for use in a human or other mammal.

As used herein, "phenoxyalkyl" is an oxygen radical bearing a phenyl substituent which bears an alkyl substituent.

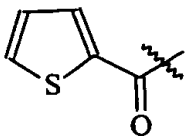
As used herein, "phenoxycarbonyl" is -C(O)O-phenyl.

As used herein, "phenylalkanoyl" is an alkanoyl radical substituted with a phenyl ring. Unless otherwise specified, phenylalkanoyls have from 7 to 10 carbon atoms.

As used herein, "phenylalkyl" is an alkyl radical bearing a phenyl substituent or a phenyl radical bearing an alkyl substituent.

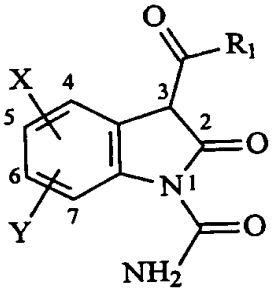
As used herein, "safe and effective amount of a compound" (or composition, or the like) means an amount that is effective to exhibit biological activity, preferably wherein the biological activity is arresting and / or reversing hair loss or promoting hair growth, at the site(s) of activity in a mammalian subject, without undue adverse side effects (such as toxicity, irritation, or allergic response), commensurate with a reasonable benefit / risk ratio when used in the manner of this invention.

As used herein, "thenoyl" is a $-C(O)SC_4H_3$ radical having the structure:

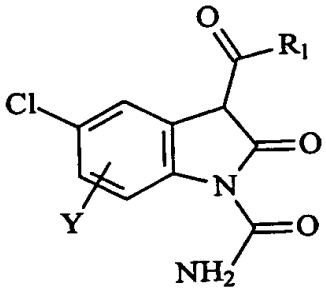


As used herein, wherein any variable, moiety, group, or the like occurs more than one time in any variable or structure, its definition at each occurrence is independent of its definition at every other occurrence.

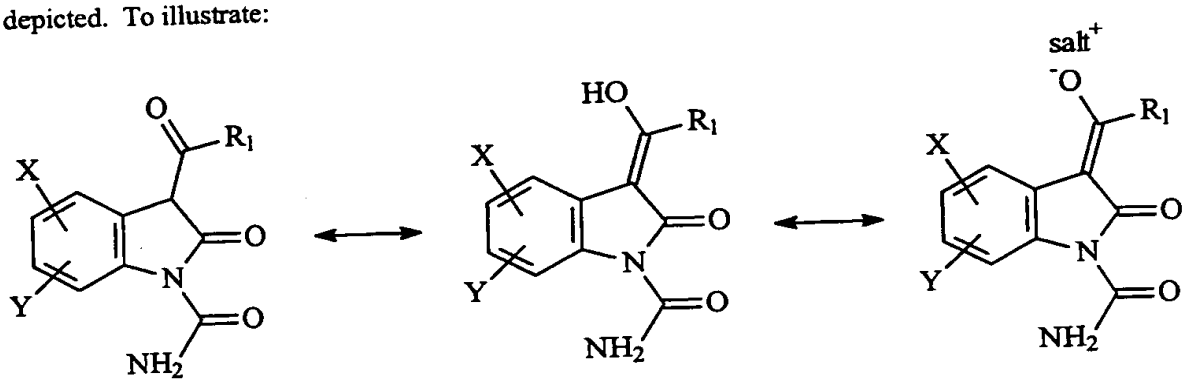
As used herein, certain substituent positions 1 through 7 will be indicated on the indoline ring of the compounds utilized herein. The position indications are as follows:



To exemplify, wherein X is chlorine and at the 5 position (X = 5-Cl) then the compound has the structure:



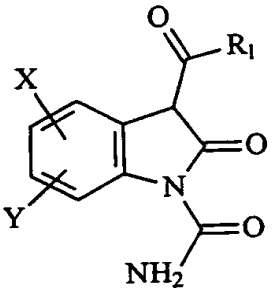
The ordinarily skilled artisan will appreciate that tautomeric forms will exist in certain compounds utilized in the present invention. Wherein tautomer A of the compound is shown, it is understood to include, for example, tautomers B and C of that compound although not specifically depicted. To illustrate:



A B C

Methods of the Present Invention

A first embodiment of the present invention relates to methods of treating hair loss comprising administering a composition comprising a compound having the structure:

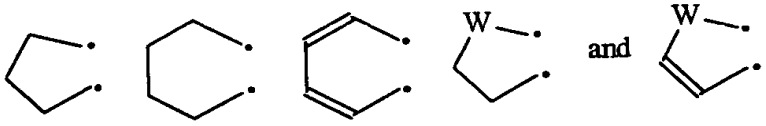


or a pharmaceutically acceptable salt, hydrate, tautomer, or biohydrolyzable amide or ester thereof, wherein:

(a) X is selected from hydrogen, fluoro, chloro, bromo, nitro, cyano, thio, alkyl having 1 to 6 carbon atoms, cycloalkyl having 3 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, alkylthio having 1 to 4 carbon atoms, trifluoromethyl, alkylsulfonyl having 1 to 4 carbon atoms, phenyl, alkanoyl having 2 to 4 carbon atoms, benzoyl, thenoyl, alkanamido having 2 to 4 carbon atoms, benzamido, and N,N-dialkylsulfamoyl;

(b) Y is selected from hydrogen, fluoro, chloro, bromo, alkyl having 1 to 4 carbon atoms, cycloalkyl having 3 to 7 carbon atoms, alkoxy having 1 to 4 carbon atoms, alkylthio having 1 to 4 carbon atoms, and trifluoromethyl;

(c) or wherein X and Y are bonded together to form a 4,5-, 5,6-, or 6,7-methylenedioxy group or a 4,5-, 5,6-, or 6,7-ethylenedioxy group; or wherein when X and Y are bonded together and attached to adjacent carbon atoms, form a divalent radical Z, wherein Z is selected from:



wherein W is selected from oxygen and sulfur;

(d) R_1 is selected from alkyl having 1 to 6 carbon atoms, cycloalkyl having 3 to 7 carbon atoms, cycloalkenyl having 4 to 7 carbons, phenyl, substituted phenyl, phenylalkyl, (substituted phenyl)alkyl, phenoxyalkyl, (substituted phenoxy)alkyl, naphthyl, bicyclo[2.2.1]heptan-2-yl, bicyclo[2.2.1]hept-5-en-2-yl, and $-(CH_2)_n-Q-R_o$; wherein there are 1 or 2 substituents on the substituted phenyl, the (substituted phenyl)alkyl, and the (substituted phenoxy)alkyl which are each, independently, selected from the group consisting of fluoro, chloro, bromo, alkyl having 1 to 4 carbon atoms, alkoxy having 1 to 4 carbon atoms, and trifluoromethyl;

(e) n is an integer selected from 0, 1, and 2;

(f) Q is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, isothiazole, oxazole, isoxazole, 1,2,3-thiadiazole, 1,3,4-thiadiazole, 1,2,5-thiadiazole, tetrahydrofuran, tetrahydrothiophene, tetrahydropyran, tetrahydrothiopyran, pyridine, pyrimidine, pyrazine, benzo[b]furan, and benzo[b]thiophene; and

(g) R_0 is selected from hydrogen, chloro, fluoro, bromo, and alkyl having 1 to 4 carbon atoms.

The X Moiety

X is selected from hydrogen, fluoro, chloro, bromo, nitro, cyano, thio, alkyl having 1 to 6 carbon atoms, cycloalkyl having 3 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, alkylthio having 1 to 4 carbon atoms, trifluoromethyl, alkylsulfonyl having 1 to 4 carbon atoms, phenyl, alkanoyl having 2 to 4 carbon atoms, benzoyl, thenoyl, alkanamido having 2 to 4 carbon atoms, benzamido, and N,N-dialkylsulfamoyl. Preferably, X is selected from hydrogen, fluoro, chloro, bromo, nitro, trifluoromethyl, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, $-SOCH_3$ (*i.e.*, alkylsulfonyl having 1 carbon atom), $-SOC_4H_9$ (*i.e.*, alkylsulfonyl having 4 carbon atoms), $-SO_2CH_3$ (*i.e.*, alkylsulfonyl having 1 carbon atom), $-SO_2C_4H_9$ (*i.e.*, alkylsulfonyl having 4 carbon atoms), methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, $-SCH_3$ (*i.e.*, alkylthio having 1 carbon atom), $-SC_4H_9$ (*i.e.*, alkylthio having 4 carbon atoms), phenyl, alkanoyl having 2 to 3 carbon atoms, benzoyl, thenoyl, alkanamido having 2 carbon atoms, $-NHCOCH(CH_3)_2$ (*i.e.*, alkanamido having 3 branched carbon atoms), benzamido, and N-N-dialkylsulfamoyl. More preferably, X is selected from hydrogen, fluoro, chloro, trifluoromethyl, methyl, and methoxy. Most preferably, X is chloro.

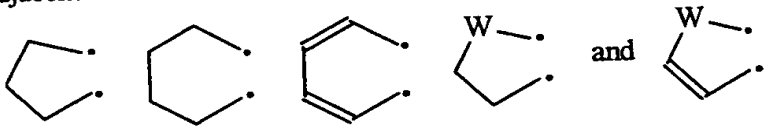
Preferably, X substitutes at position 4, 5, or 6 of the indoline ring as defined herein above. More preferably, X substitutes at position 5 or 6 of the indoline ring as defined herein above. Most preferably, X substitutes at position 5 of the indoline ring as defined herein above.

The Y Moiety

Y is selected from hydrogen, fluoro, chloro, bromo, alkyl having 1 to 4 carbon atoms, cycloalkyl having 3 to 7 carbon atoms, alkoxy having 1 to 4 carbon atoms, alkylthio having 1 to 4 carbon atoms, and trifluoromethyl. Preferably, Y is selected from hydrogen, fluoro, chloro, bromo, methyl (*i.e.*, alkyl having 1 carbon atom), and methoxy (*i.e.*, alkoxy having 1 carbon atom). Most preferably, Y is hydrogen.

Preferably, Y substitutes at position 5 or 6 of the indoline ring as defined herein above. Most preferably, Y substitutes at position 6 of the indoline ring as defined herein above.

Alternatively, X and Y are bonded together to form a 4,5-, 5,6-, or 6,7-methylenedioxy group or a 4,5-, 5,6-, or 6,7-ethylenedioxy group; or wherein when X and Y are bonded together and attached to adjacent carbon atoms, form a divalent radical Z, wherein Z is selected from:



wherein W is selected from oxygen and sulfur, preferably oxygen.

The R_1 Moiety

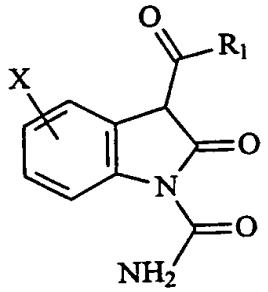
R_1 is selected from alkyl having 1 to 6 carbon atoms, cycloalkyl having 3 to 7 carbon atoms, cycloalkenyl having 4 to 7 carbons, phenyl, substituted phenyl, phenylalkyl, phenoxyalkyl, (substituted phenoxy)alkyl, naphthyl, bicyclo[2.2.1]heptan-2-yl, bicyclo[2.2.1]hept-5-en-2-yl, and $-(CH_2)_n-Q-R_0$; wherein there are 1 or 2 substituents on the substituted phenyl, the (substituted phenyl)alkyl, and the (substituted phenoxy)alkyl which are each, independently, selected from the group consisting of fluoro, chloro, bromo, alkyl having 1 to 4 carbon atoms, alkoxy having 1 to 4 carbon atoms, and trifluoromethyl. The integer n is 0, 1, or 2 (wherein n is 0, then $-(CH_2)_n-Q-R_0$ is $-Q-R_0$). Q is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, isothiazole, oxazole, isoxazole, 1,2,3-thiadiazole, 1,3,4-thiadiazole, 1,2,5-thiadiazole, tetrahydrofuran, tetrahydrothiophene, tetrahydropyran, tetrahydrothiopyran, pyridine, pyrimidine, pyrazine, benzo[b]furan, and benzo[b]thiophene. R_0 is selected from hydrogen, chloro, fluoro, bromo, and alkyl having 1 to 4 carbon atoms.

Preferably, R_1 is $-(CH_2)_n-Q-R_0$. Q is preferably selected from furan, thiophene, and pyrrole. Most preferably, Q is thiophene. Wherein R_1 is $-(CH_2)_n-Q-R_0$, then n is preferably 0 or 1, most preferably 0. Preferably, R_0 is hydrogen.

Examples of preferred moieties for R_1 include trifluoromethyl, 2-furyl, (2-furyl)methyl, 3-methyl-2-furyl, 5-propyl-2-furyl, 3-furyl, (2-thienyl)methyl, (3-thienyl)methyl, 3-methyl-2-thienyl, 5-propyl-2-thienyl, 3-(3-thienyl)propyl, 1-(2-furyl)ethyl, 3-(2-furyl)propyl, 2-thienyl, 3-thienyl, methyl, *iso*-propyl, *n*-hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclobut-1-en-1-yl, cyclohep-1-en-1-yl, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 3-*n*-butyl-phenyl, 3-methoxyphenyl, 4-isobutoxyphenyl, 2,4-dichlorophenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-isopropoxyphenyl, 4-chlorophenoxy, benzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, phenoxymethyl, (3-fluorophenoxy)methyl, (4-bromophenoxy)methyl, 2-(methylphenoxy)methyl, (4-isobutylphenoxy)methyl, (3-methoxyphenoxy)methyl, (4-butoxyphenoxy)methyl, (thiophenoxy)methyl, 4-(chlorophenoxy)methyl, (4-thiazolyl)methyl, 1-methyl-1-phenylethyl, 2-(2-tolyl)ethyl, 1-

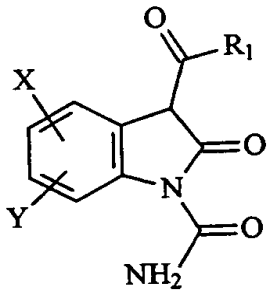
phenoxyethyl, 2-(3-thienyl)ethyl, 2-(4-isopropylphenyl)ethyl, 3-(phenyl)propyl, 3-(thiophenoxy)propyl, 3-(phenoxy)propyl, 3-(3-chlorophenyl)propyl, bicyclo[2.2.1]heptan-2-yl, bicyclo[2.2.1]hept-2-en-5-yl, 1-(phenyl)ethyl, 2-(phenyl)ethyl, 2-pyrrolyl, 5-pyrimidinyl, 4-pyridyl, 3-tetrahydrothienyl, 3-trifluoromethylbenzyl, 5-methyl-3-isoxazolyl, 5-methyl-4-isoxazolyl, 1,2,3-thiadiazol-4-yl, 1,2,5-thiadiazol-3-yl, 2-tetrahydrofuryl, 2-tetrahydropyranyl, 4-isothiazolyl, 2-thiazolyl, 1-imidazolyl, 1-naphthyl, 2-pyrazinyl, 2-*n*-propyl-4-thiazolyl, 2-oxazolyl, 2-isoxazolyl, and 1,3,4-thiadiazol-2-yl. The most preferred among these examples is 2-thienyl.

Table 1 - Preferred Compounds for Use in the Present Invention



X	R_1
5-Cl	2-furyl
5-Cl	2-(2-thienyl)methyl
5-Cl	2-thienyl
6-Cl	2-furyl
6-Cl	2-thienyl
6-Cl	2-(2-thienyl)methyl
5-F	2-furyl
5-F	2-thienyl
5-F	2-(2-thienyl)methyl
6-F	2-furyl
6-F	2-thienyl
6-F	2-(2-thienyl)methyl
5-CF_3	2-furyl
5-CF_3	2-thienyl
5-CF_3	2-(2-thienyl)methyl
6-CF_3	2-furyl
6-CF_3	2-thienyl

Table 2 - Preferred Compounds for Use in the Present Invention



X	Y	R_1
H	H	2-furyl
H	H	2-thienyl
H	H	2-(2-thienyl)methyl
H	H	cyclohexyl
H	H	*iso*-propyl
H	H	cyclopropyl
H	H	phenoxymethyl
H	H	4-(chlorophenoxy)methyl
H	H	methyl
5-Cl	H	cyclohexyl
5-F	H	phenoxymethyl
5-F	H	*iso*-propyl
5-F	H	cyclohexyl
5-Cl	H	iso-propyl
5-Cl	H	cyclopropyl
6-F	H	bicyclo[2.2.1]heptan-2-yl
4-Cl	H	2-thienyl
4-Cl	H	2-furyl
$5\text{-}CH_3$	6-F	2-furyl
6-F	H	methyl
$5\text{-}OCH_3$	$6\text{-}OCH_3$	methyl
$5\text{-}OCH_3$	$6\text{-}OCH_3$	2-thienyl
6-Cl	H	cyclohexyl
$5\text{-}CF_3$	H	*iso*-propyl
5-F	H	cyclopropyl
H	H	4-chlorophenyl

H	H	4-methylphenyl
H	H	benzyl
H	H	1-(phenyl)ethyl
5-CF_3	H	cyclopropyl
5-CF_3	H	cyclohexyl
5-CF_3	H	methyl
5-CF_3	H	phenyl
5-CF_3	H	4-chlorophenyl
5-CF_3	H	4-methylphenyl
6-CF_3	H	*iso*-propyl
6-CF_3	H	bicyclo[2.2.1]heptan-2-yl
6-SCH_3	H	(2-thienyl)methyl
4-SCH_3	H	bicyclo[2.2.1]heptan-2-yl
6-F	H	*iso*-propyl
6-SCH_3	H	bicyclo[2.2.1]heptan-2-yl
5-CF_3	H	benzyl
5-CF_3	H	1-(phenyl)ethyl
5-CF_3	H	phenoxymethyl
5-CH_3	6-CH_3	2-furyl
4-CH_3	5-CH_3	2-furyl
5-CH_3	6-CH_3	2-thienyl
4- CH_3	5- CH_3	2-thienyl
5-CH_3	6- CH_3	(2-thienyl)methyl
5-Cl	H	phenyl
5-Cl	H	4-chlorophenyl
5-Cl	H	4-methylphenyl
5-Cl	H	benzyl
6-Cl	H	benzyl
4-Cl	H	cyclohexyl
4-Cl	H	*iso*-propyl
4-SCH_3	H	2-furyl
6-Br	H	bicyclo[2.2.1]heptan-2-yl
5-CH_3	H	(2-thienyl)methyl
6-Cl	H	4-chlorophenyl
5-CH_3	H	phenyl

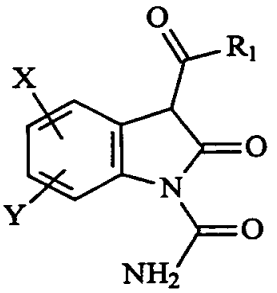
5-OCH_3	H	4-chlorophenyl
5-OCH_3	H	phenyl
5-CH_3	H	cyclohexyl
4-Cl	H	methyl
5-OCH_3	H	*iso*-propyl
5-OCH_3	H	cyclohexyl
5-CH_3	H	methyl
5-Cl	H	cyclopentyl
5-Cl	H	cyclobutyl
5-CF_3	H	cyclopentyl
6-Cl	H	cyclobutyl
6-Cl	H	cyclopentyl
5-Cl	H	1-phenylethyl
5-Cl	H	phenoxymethyl
5-F	H	bicyclo[2.2.1]heptan-2-yl
5-CF_3	H	bicyclo[2.2.1]heptan-2-yl
6-Br	H	2-furyl
6-Cl	H	1-(phenyl)ethyl
5-NO_2	H	2-thienyl
5-NO_2	H	benzyl
5-OCH_3	H	1-(phenyl)ethyl
5-OCH_3	H	2-thienyl
6-Cl	H	phenyl
5-CH_3	H	4-chlorophenyl
H	H	2-pyrrolyl
5-Cl	H	2-pyrrolyl
5-F	H	3-thienyl
5-Cl	H	3-thienyl
5-F	H	3-furyl
5-Cl	H	3-furyl
6-Cl	H	3-furyl
5-CF_3	H	3-furyl
5-F	H	(3-thienyl)methyl
5-Cl	H	(3-thienyl)methyl
6-Cl	H	(3-thienyl)methyl

5-CF_3	H	(3-thienyl)methyl
5-Cl	6-Cl	2-thienyl
5-Cl	6-Cl	(2-thienyl)methyl
6-C_6H_5	H	2-thienyl
6-C_6H_5	H	(2-thienyl)methyl
H	H	2,4-dichlorophenyl
5-Cl	H	trifluoromethyl
5-CH_3	H	2-furyl
5-CH_3	H	benzyl
5-CH_3	H	2-thienyl
5-OCH_3	H	(2-thienyl)methyl
5-Cl	H	bicyclo[2.2.1]heptan-2-yl
5-CF_3	H	trifluoromethyl
5-OCH_3	H	benzyl
5-OCH_3	H	methyl
5-CF_3	H	3-thienyl
6-Cl	H	(3-thienyl)methyl
H	H	5-pyrimidinyl
5-Cl	H	bicyclo[2.2.1]hept-2-en-5-yl
H	H	bicyclo[2.2.1]hept-2-en-5-yl
6-Cl	H	bicyclo[2.2.1]hept-2-en-5-yl
5-Cl	H	1-phenylethyl
5-CF_3	H	1-phenylethyl
5-Cl	H	1-phenylethyl
5-CF_3	H	1-phenylethyl
5-CF_3	H	3-trifluoromethylbenzyl
6-Cl	H	3-trifluoromethylbenzyl
H	H	2-chlorobenzyl
5-Cl	H	2-chlorobenzyl
5-F	H	2-chlorobenzyl
5-CF_3	H	2-chlorobenzyl
5-F	H	3-trifluoromethylbenzyl

6-Cl	H	3-thienyl
6-Cl	H	2-chlorobenzyl
5-Cl	H	4-chlorobenzyl
6-Cl	H	4-chlorobenzyl
5-F	H	4-chlorobenzyl
5-Cl	H	3-chlorobenzyl
5-F	H	3-chlorobenzyl
H	H	3-trifluoromethylbenzyl
5-C_6H_5CO	H	benzyl
5-C_6H_5CO	H	(2-thienyl)methyl
5-C_6H_5CO	H	2-thienyl
5-CH_3CO	H	benzyl
5-C_4H_3SCO (thenoyl)	H	(2-thienyl)methyl
6-F	H	5-methyl-3-isoxazolyl
5-Cl	H	5-methyl-3-isoxazolyl
5-CH_3CO	H	(2-thienyl)methyl
5-C_4H_3SCO (thenoyl)	H	benzyl
5-F	H	5-methyl-3-isoxazolyl
5-F	6-Cl	(2-thienyl)methyl
5-F	6-Cl	2-furyl
5-F	6-Cl	2-thienyl
5-Cl	H	1,2,3-thiadiazol-4-yl
6-F	H	1,2,3-thiadiazol-4-yl
5-F	6-Cl	benzyl
6-CF_3	H	1-phenylethyl
6-F	H	1-phenylethyl
5-Cl	H	1-phenoxyethyl
6-F	H	1-phenoxyethyl
6-F	H	2-phenylethyl
5-Cl	H	2-phenylethyl
5-F	6-F	2-furyl
5-F	6-F	benzyl
5-F	6-F	(2-thienyl)methyl
5-NO_2	H	2-furyl
5-NO_2	H	(2-thienyl)methyl

5-Cl	H	3-trifluoromethylbenzyl
5-NO_2	H	1-phenylethyl
5-Cl	H	(2-furyl)methyl
6-F	H	(2-furyl)methyl
6-F	H	1,2,5-thiadiazol-3-yl
5-Cl	H	1,2,5-thiadiazol-3-yl
6-CF_3	H	1-phenylethyl
6-F	H	1-phenylethyl
6-CF_3	H	(2-thienyl)methyl
5-F	6-Cl	2-tetrahydrofuryl
5-NO_2	H	2-tetrahydrofuryl
5-Cl	H	4-isothiazolyl
5-Cl	H	2-thiazolyl

Table 3 - Preferred Compounds for Use in the Present Invention

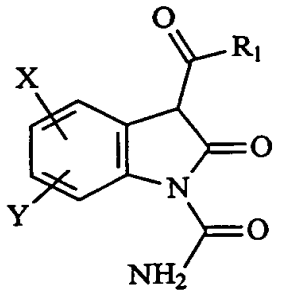


X	Y	R_1
5-*n*-OC_4H_9	H	2-furyl
5-OC_2H_5	H	2-thienyl
7-Cl	H	(2-thienyl)methyl
6-F	H	*n*-hexyl
5-F	H	cycloheptyl
5-Cl	H	2-fluorophenyl
5-*n*-C_4H_9	H	2-furyl
5-CH_3	H	4-bromophenyl
6-SCH_3	H	3-*n*-butylphenyl
5-CF_3	H	3-methoxyphenyl
5-*n*-SC_4H_9	H	4-isobutoxyphenyl
5-CH_3	6-CH_3	3-(phenyl)propyl

6-OCH_3	H	3-(phenoxy)propyl
6-SCH_3	H	2-thienyl
5-NO_2	H	(3-fluorophenoxy)methyl
H	H	cyclobut-1-en-1-yl
5-Cl	H	cyclohep-1-en-1-yl
6-F	H	(thiophenoxy)methyl
5-CF_3	H	3-(thiophenoxy)propyl
H	H	1-imidazolyl
5-Cl	6-Cl	2-tetrahydropyranyl
6-*n*-SC_4H_9	H	(4-chlorophenoxy)methyl
5-OCH_3	6-OCH_3	(2-thienyl)methyl
5-Cl	H	(2-furyl)methyl
5-F	6-Cl	(4-bromophenoxy)methyl
5-F	6-Cl	2-tetrahydrothiopyranyl
6-Cl	H	(2-methylphenoxy)methyl
6-Br	H	(4-isobutylphenoxy)methyl
6-*n*-SC_4H_9	H	2-thienyl
7-Cl	H	(3-methoxyphenoxy)methyl
4-SCH_3	H	(4-butoxyphenoxy)methyl
5-NO_2	H	3-furyl
4-CH_3	5-CH_3	3-thienyl
6-SCH_3	H	3-methyl-2-furyl
7-Cl	H	5-propyl-2-furyl
5-$CH(CH_3)_2$	H	3-methyl-2-thienyl
5-F	6-Cl	5-propyl-2-thienyl
5-NO_2	H	3-(3-thienyl)propyl
5-OC_2H_5	H	1-(2-furyl)ethyl
7-Cl	H	3-(2-furyl)propyl
6-CH_3SO	H	2-thienyl
6-*n*-C_4H_9SO	H	2-furyl
4-CH_3SO_2	H	3-fluorophenyl
6-*n*-$C_4H_9SO_2$	H	2-thiazolyl
5-NO_2	H	2-(3-thienyl)ethyl
6-C_6H_5	H	4-chlorophenyl
H	5-Br	2-(2-tolyl)ethyl

5-CH_3CO	H	4-trifluoromethylphenyl
6-*n*-C_3H_7CO	H	4-isothiazolyl
5-Cl	H	1-naphthyl
5-C_6H_5CO	H	1,2,3-thiadiazol-4-yl
5-C_4H_3SCO (thenoyl)	H	3-(3-chlorophenyl)propyl
6-CF_3	H	(4-thiazolyl)methyl
6-F	H	1,2,5-thiadiazol-3-yl
5-CH_3CONH	H	1-methyl-1-phenylethyl
5-Cl	6-Cl	5-methyl-4-isoxazolyl
5-$(CH_3)_2CH$-CONH	H	2-(4-isopropylphenyl)ethyl
5-C_6H_5CONH	H	2-thienyl
5-CH_3	6-CH_3	4-isopropoxyphenyl
5-$SO_2N(CH_3)_2$	H	benzyl
5-F	6-F	4-chlorophenoxy
5-$SO_2N(n\text{-}C_3H_7)_2$	H	2-tetrahydrofuryl
H	4-Cl	4-pyridyl
6-Cl	H	3-tetrahydrothienyl
H	H	5-pyrimidyl
5-CH_3	6-F	2-pyrazinyl
H	H	2-*n*-propyl-4-thiazolyl
5-Br	H	2-oxazolyl
H	H	3-isoxazolyl
H	H	1,3,4-thiadiazol-2-yl

Table 4 - Preferred Compounds for Use in the Present Invention

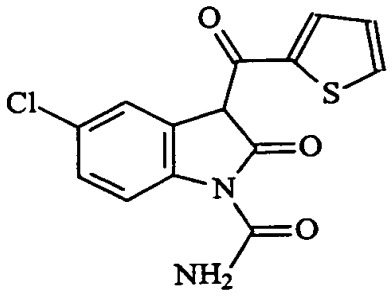


X and Y**	R_1
4-CH_2-CH_2-CH_2-5	2-furyl
5-CH_2-CH_2-CH_2-6	2-thienyl

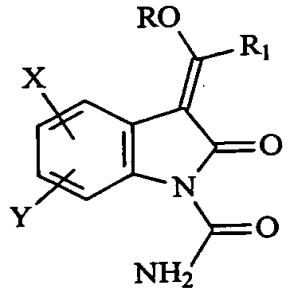
6-CH_2-CH_2-CH_2-CH_2-7	2-furyl
5-CH=CH-CH=CH-6	(2-thienyl)methyl
5-O-CH_2-CH_2-6	2-thienyl
5-CH_2-CH_2-O-6	2-furyl
5-S-CH_2-CH_2-6	2-thienyl
5-O-CH=CH-6	2-furyl
5-S-CH=CH-6	(2-thienyl)methyl
5-CH=CH-S-6	2-furyl

**In this column of Table 4, the numeral to the left of the formula indicates the point of attachment of that end of the formula to the respective position on the indoline ring. The numeral to the right of the formula indicates the point of attachment of that end of the formula to the respective position on the indoline ring. The position numbers on the indoline ring are defined herein above. Thus, for the compounds set forth in Table 4, X and Y are bonded together.

A particularly preferred compound for use in the present invention is known as tenidap (5-chloro-3-(2-thenoyl)-2-oxindole-1-carboxamide) (including salts, hydrates tautormers, and biohydrolyzable amides and esters thereof), having the structure:



In a further preferred embodiment of the present invention, pro-forms of the above described compounds are utilized (the term "pro-drug" is also commonly used in the art; as used herein, the terms "pro-form" and "pro-drug" should be considered synonymous). The pro-forms are, for example, enol ethers and esters of the above described compounds. Without intending to be limited by theory, it is contemplated that the pro-forms are precursors which, following administration, release a biologically active compound *in vivo* through, for example, hydrolysis of an ether or ester of the pro-form. The pro-forms have the structure:

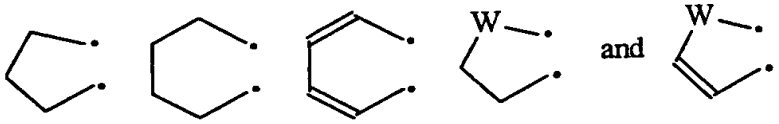


or a pharmaceutically acceptable salt, hydrate, or tautomer thereof, wherein:

(a) X is selected from hydrogen, fluoro, chloro, bromo, nitro, cyano, thio, alkyl having 1 to 6 carbon atoms, cycloalkyl having 3 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, alkylthio having 1 to 4 carbon atoms, trifluoromethyl, alkylsulfonyl having 1 to 4 carbon atoms, phenyl, alkanoyl having 2 to 4 carbon atoms, benzoyl, thenoyl, alkanamido having 2 to 4 carbon atoms, benzamido, and N,N-dialkylsulfamoyl;

(b) Y is selected from hydrogen, fluoro, chloro, bromo, alkyl having 1 to 4 carbon atoms, cycloalkyl having 3 to 7 carbon atoms, alkoxy having 1 to 4 carbon atoms, alkylthio having 1 to 4 carbon atoms, and trifluoromethyl;

(c) or wherein X and Y are bonded together to form a 4,5-, 5,6-, or 6,7-methylenedioxy group or a 4,5-, 5,6-, or 6,7-ethylenedioxy group; or wherein when X and Y are bonded together and attached to adjacent carbon atoms, form a divalent radical Z, wherein Z is selected from:



wherein W is selected from oxygen and sulfur;

(d) R_1 is selected from alkyl having 1 to 6 carbon atoms, cycloalkyl having 3 to 7 carbon atoms, cycloalkenyl having 4 to 7 carbons, phenyl, substituted phenyl, phenylalkyl, (substituted phenyl)alkyl, phenoxyalkyl, (substituted phenoxy)alkyl, naphthyl, bicyclo[2.2.1]heptan-2-yl, bicyclo[2.2.1]hept-5-en-2-yl, and $-(CH_2)_n-Q-R_0$; wherein there are 1 or 2 substituents on the substituted phenyl, the (substituted phenyl)alkyl, and the (substituted phenoxy)alkyl which are each, independently, selected from the group consisting of fluoro, chloro, bromo, alkyl having 1 to 4 carbon atoms, alkoxy having 1 to 4 carbon atoms, and trifluoromethyl;

(e) n is an integer selected from 0, 1, and 2;

(f) Q is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, isothiazole, oxazole, isoxazole, 1,2,3-thiadiazole, 1,3,4-thiadiazole, 1,2,5-thiadiazole, tetrahydrofuran, tetrahydrothiophene, tetrahydropyran, tetrahydrothiopyran, pyridine, pyrimidine, pyrazine, benzo[b]furan, and benzo[b]thiophene;

(g) R_0 is selected from hydrogen, chloro, fluoro, bromo, and alkyl having 1 to 4 carbon atoms; and

(h) R is selected from alkanoyl having 2 to 10 carbon atoms, phenylalkanoyl having 7 to 10 carbon atoms, alkoxycarbonyl having 2 to 10 carbon atoms, phenoxycarbonyl, alkylsulfonyl having 1 to 4 carbon atoms, and alkyl having 1 to 4 carbon atoms.

All isomers of the exocyclic double bond depicted for the above pro-forms are contemplated within the methods of the present invention (including *cis*, *trans*, and mixtures thereof).

The X Moiety

In the pro-form compounds utilized in the present invention, X is selected from hydrogen, fluoro, chloro, bromo, nitro, cyano, thio, alkyl having 1 to 6 carbon atoms, cycloalkyl having 3 to 8 carbon atoms, alkoxy having 1 to 4 carbon atoms, alkylthio having 1 to 4 carbon atoms, trifluoromethyl, alkylsulfonyl having 1 to 4 carbon atoms, phenyl, alkanoyl having 2 to 4 carbon atoms, benzoyl, thenoyl, alkanamido having 2 to 4 carbon atoms, benzamido, and N,N-dialkylsulfamoyl. Preferably, X is selected from hydrogen, fluoro, chloro, bromo, nitro, trifluoromethyl, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, $-SOCH_3$ (*i.e.*, alkylsulfonyl having 1 carbon atom), $-SOC_4H_9$ (*i.e.*, alkylsulfonyl having 4 carbon atoms), $-SO_2CH_3$ (*i.e.*, alkylsulfonyl having 1 carbon atom), $-SO_2C_4H_9$ (*i.e.*, alkylsulfonyl having 4 carbon atoms), methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, $-SCH_3$ (*i.e.*, alkylthio having 1 carbon atom), $-SC_4H_9$ (*i.e.*, alkylthio having 4 carbon atoms), phenyl, alkanoyl having 2 to 3 carbon atoms, thenoyl, alkanamido having 2 carbon atoms, $-NHCOCH(CH_3)_2$ (*i.e.*, alkanamido having 3 branched carbon atoms), benzamido, and N-N-dialkylsulfamoyl. More preferably, X is selected from hydrogen, fluoro, and chloro. Most preferably, X is chloro.

Preferably, in the pro-form compounds, X substitutes at position 5 or 6 of the indoline ring as defined herein above. Most preferably, X substitutes at position 5 of the indoline ring as defined herein above.

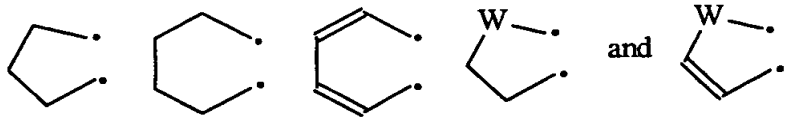
The Y Moiety

In the pro-form compounds utilized in the present invention, Y is selected from hydrogen, fluoro, chloro, bromo, alkyl having 1 to 4 carbon atoms, cycloalkyl having 3 to 7 carbon atoms, alkoxy having 1 to 4 carbon atoms, alkylthio having 1 to 4 carbon atoms, and trifluoromethyl. In the pro-form compounds utilized herein, Y is preferably selected from hydrogen, fluoro, and chloro. Most preferably, Y is hydrogen for the pro-form compounds herein.

Preferably, Y substitutes at position 5 or 6 of the indoline ring as defined herein above. Most preferably, Y substitutes at position 6 of the indoline ring as defined herein above.

Alternatively, in the pro-form compounds herein, X and Y are bonded together to form a 4,5-, 5,6-, or 6,7-methylenedioxy group or a 4,5-, 5,6-, or 6,7-ethylenedioxy group; or wherein

when X and Y are bonded together and attached to adjacent carbon atoms, form a divalent radical Z, wherein Z is selected from:



wherein W is selected from oxygen and sulfur, preferably oxygen.

The R_1 Moiety

In the pro-form compounds utilized in the present invention, R_1 is selected from alkyl having 1 to 6 carbon atoms, cycloalkyl having 3 to 7 carbon atoms, cycloalkenyl having 4 to 7 carbons, phenyl, substituted phenyl, phenylalkyl, phenoxyalkyl, (substituted phenoxy)alkyl, naphthyl, bicyclo[2.2.1]heptan-2-yl, bicyclo[2.2.1]hept-5-en-2-yl, and $-(CH_2)_n-Q-R_0$; wherein there are 1 or 2 substituents on the substituted phenyl, the (substituted phenyl)alkyl, and the (substituted phenoxy)alkyl which are each, independently, selected from the group consisting of fluoro, chloro, bromo, alkyl having 1 to 4 carbon atoms, alkoxy having 1 to 4 carbon atoms, and trifluoromethyl. In the pro-form compounds herein, the integer n is 0, 1, or 2 (wherein n is 0, then $-(CH_2)_n-Q-R_0$ is $-Q-R_0$). In the pro-form compounds herein, Q is selected from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, isothiazole, oxazole, isoxazole, 1,2,3-thiadiazole, 1,3,4-thiadiazole, 1,2,5-thiadiazole, tetrahydrofuran, tetrahydrothiophene, tetrahydropyran, tetrahydrothiopyran, pyridine, pyrimidine, pyrazine, benzo[b]furan, and benzo[b]thiophene. In the pro-form compounds herein, R_0 is selected from hydrogen, chloro, fluoro, bromo, and alkyl having 1 to 4 carbon atoms.

Preferably, R_1 is $-(CH_2)_n-Q-R_0$ or benzyl for the pro-form compounds herein. Q is preferably selected from furan, thiophene, and pyrrole. Most preferably, Q is thiophene. Wherein R_1 is $-(CH_2)_n-Q-R_0$, then n is preferably 0 or 1, most preferably 0. Preferably, R_0 is hydrogen. In the pro-form compounds herein, R_1 is most preferably $-(CH_2)_n-Q-R_0$.

In the pro-form compounds herein, examples of preferred moieties for R_1 include trifluoromethyl, 2-furyl, (2-furyl)methyl, 3-methyl-2-furyl, 5-propyl-2-furyl, 3-furyl, (2-thienyl)methyl, (3-thienyl)methyl, 3-methyl-2-thienyl, 5-propyl-2-thienyl, 3-(3-thienyl)propyl, 1-(2-furyl)ethyl, 3-(2-furyl)propyl, 2-thienyl, 3-thienyl, methyl, *iso*-propyl, *n*-hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclobut-1-en-1-yl, cyclohep-1-en-1-yl, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 3-*n*-butyl-phenyl, 3-methoxyphenyl, 4-isobutoxyphenyl, 2,4-dichlorophenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-isopropoxyphenyl, 4-chlorophenoxy, benzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, phenoxymethyl, (3-fluorophenoxy)methyl, (4-bromophenoxy)methyl, 2-(methylphenoxy)methyl, (4-isobutylphenoxy)methyl, (3-methoxyphenoxy)methyl, (4-butoxyphenoxy)methyl, (thiophenoxy)methyl, 4-(chlorophenoxy)methyl, (4-thiazolyl)methyl, 1-methyl-1-phenylethyl, 2-

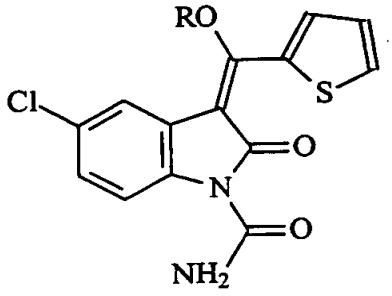
(2-tolyl)ethyl, 1-phenoxyethyl, 2-(3-thienyl)ethyl, 2-(4-isopropylphenyl)ethyl, 3-(phenyl)propyl, 3-(thiophenoxy)propyl, 3-(phenoxy)propyl, 3-(3-chlorophenyl)propyl, bicyclo[2.2.1]heptan-2-yl, bicyclo[2.2.1]hept-2-en-5-yl, 1-(phenyl)ethyl, 2-(phenyl)ethyl, 2-pyrrolyl, 5-pyrimidinyl, 4-pyridyl, 3-tetrahydrothienyl, 3-trifluoromethylbenzyl, 5-methyl-3-isoxazolyl, 5-methyl-4-isoxazolyl, 1,2,3-thiadiazol-4-yl, 1,2,5-thiadiazol-3-yl, 2-tetrahydrofuryl, 2-tetrahydropyranyl, 4-isothiazolyl, 2-thiazolyl, 1-imidazolyl, 1-naphthyl, 2-pyrazinyl, 2-*n*-propyl-4-thiazolyl, 2-oxazolyl, 2-isoxazolyl, and 1,3,4-thiadiazol-2-yl. The most preferred among these examples is 2-thienyl.

The R Moiety

In the pro-form compounds utilized herein, R is selected from alkanoyl having 2 to 10 carbon atoms, phenylalkanoyl having 7 to 10 carbon atoms, alkoxycarbonyl having 2 to 10 carbon atoms, phenoxycarbonyl, alkylsulfonyl having 1 to 4 carbon atoms, and alkyl having 1 to 4 carbon atoms. Preferably, R is selected from alkanoyl having 2 to 10 carbon atoms, phenylalkanoyl having 7 to 10 carbon atoms, alkoxycarbonyl having 2 to 10 carbon atoms, phenoxycarbonyl, and alkyl having 1 to 3 carbon atoms. More preferably, R is selected from alkanoyl having 2 to 4 carbon atoms, phenylalkanoyl having 7 to 10 carbon atoms, and alkyl having 1 to 3 carbon atoms. Most preferably, R is selected from alkanoyl having 2 to 4 carbon atoms and alkyl having 1 to 3 carbon atoms.

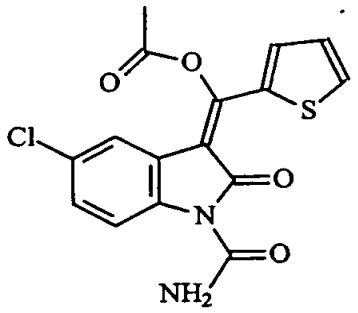
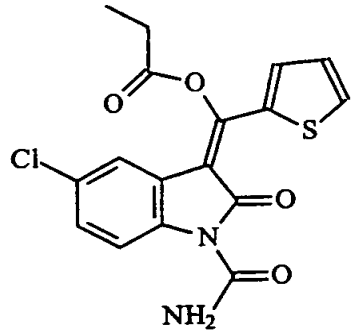
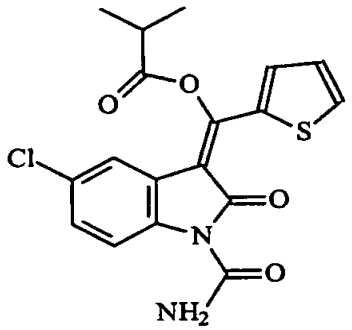
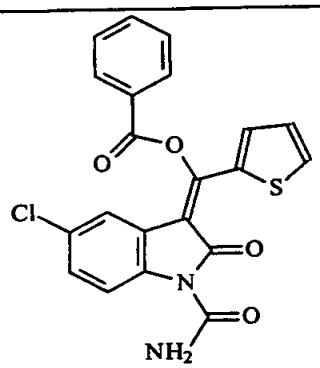
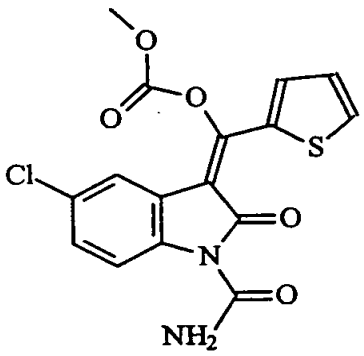
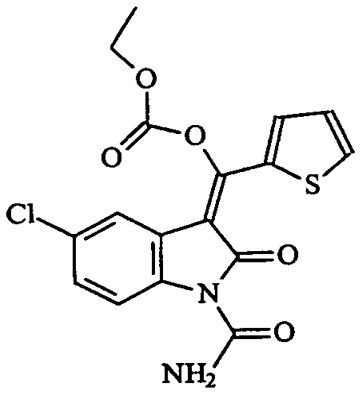
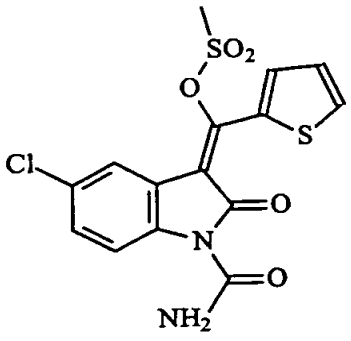
Non-limiting examples of R include acetyl, propionyl, *i*-butyryl, phenylacetyl, methoxycarbonyl, ethoxycarbonyl, *n*-hexoxycarbonyl, and methylsulfonyl.

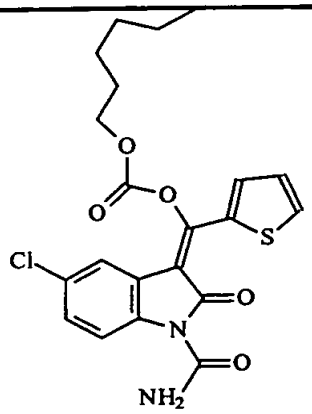
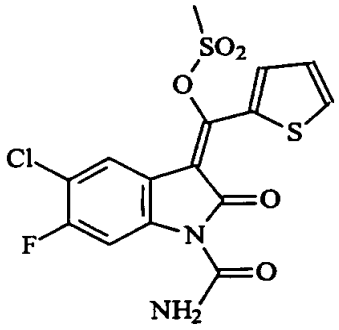
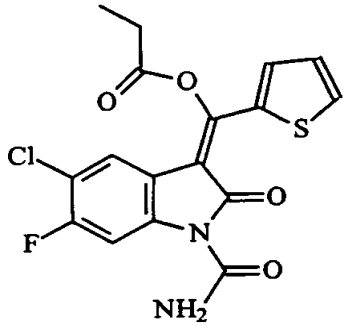
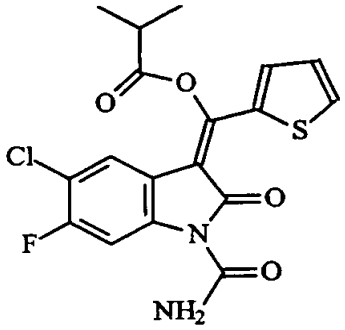
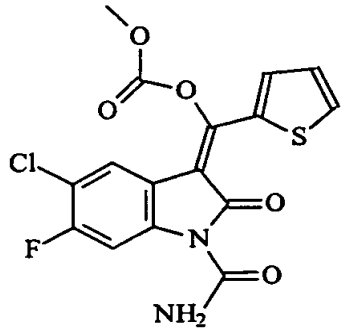
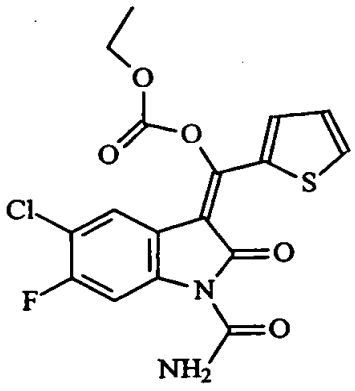
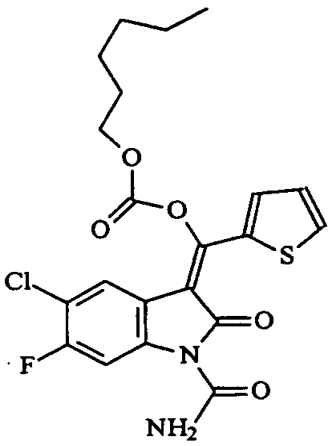
Particularly preferred pro-forms utilized in the present invention include the pro-forms of tenidap (5-chloro-3-(2-thenoyl)-2-oxindole-1-carboxamide) (and salts, hydrates, and tautomers thereof). Such pro-forms will have the structure:

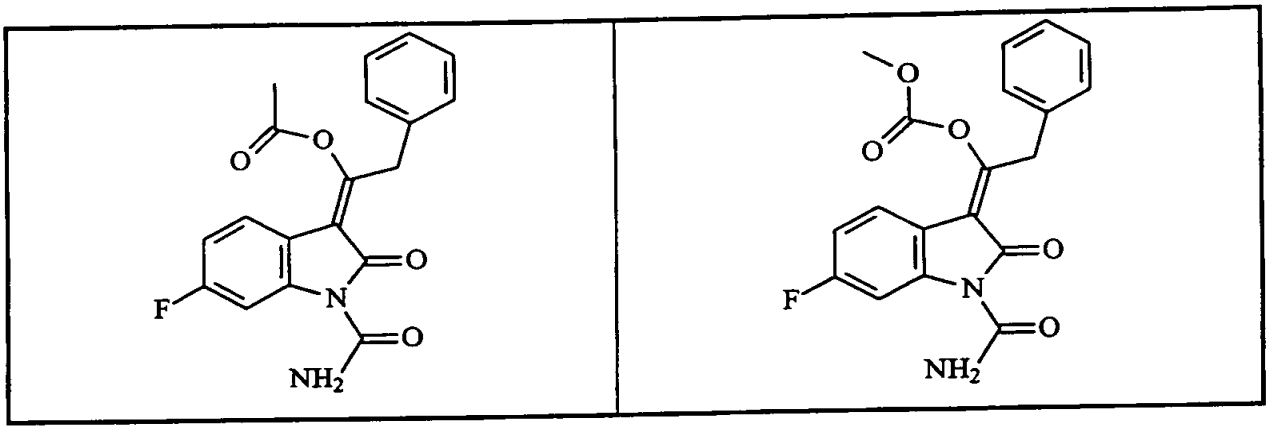


Other non-limiting examples of pro-form compounds suitable for use in the present invention are set forth in Table 5 below:

Table 5 - Preferred Compounds for Use in the Present Invention

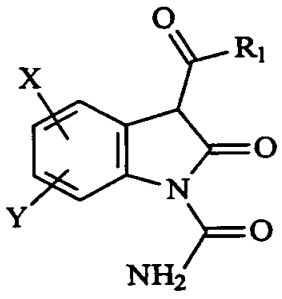
	
	
	
	

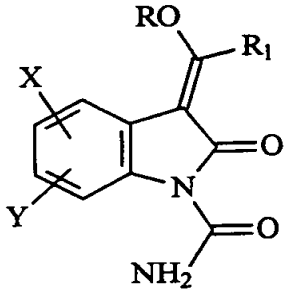


Other preferred compounds (including salts, hydrates, tautomers, and biohydrolyzable amides and esters) useful in the methods of the present invention are those described in Kadin, U.S. Patent No. 4,556,672, assigned to Pfizer Inc., issued December 3, 1985; Reiter et al., WO 90/04393, published May 3, 1990; Schulte et al., U.S. Patent No. 5,059,693, assigned to Pfizer et al., issued October 22, 1991; Allen et al., EP 277,738, assigned to Pfizer Inc., issued March 18, 1992; Loose et al., U.S. Patent No. 5,545,656, assigned to Pfizer Inc., issued August 13, 1996; Blasko et al., WO 97/36895, published October 9, 1997; Ahmed, WO 97/22605, assigned to Pfizer Inc., published June 26, 1997; and Ahmed, EP 0,826,685, assigned to Pfizer Inc., published March 4, 1998; all of which are herein incorporated by reference in their entirety.

As stated above, the compounds contemplated for use within the present invention, *i.e.*, those of structures:



and



may be administered as one or more salts. Many such salts are known in the art. Such acceptable salts must, when administered, be appropriate for mammalian use. Such salts may be formed as described in Kadin, U.S. Patent No. 4,556,672, assigned to Pfizer Inc., issued December 3, 1985. Such salts include, for example, both organic and inorganic salts. Non-limiting examples of suitable salts include salts formed with ammonia, organic amines, alkali metal hydroxides, alkali metal carbonates, alkali metal bicarbonates, alkali metal hydrides, alkali metal alkoxides, alkaline earth metal hydroxides, alkaline earth metal carbonates, alkaline earth metal hydrides, and alkaline earth metal alkoxides. Representative examples of bases which may form such salts include ammonia, primary amines such as *n*-propylamine, *n*-butylamine, aniline, cyclohexylamine, benzylamine, *p*-toluidine, ethanolamine, and glucamine; secondary amines such as diethylamine

diethanolamine, N-methylglucamine, N-methylaniline, morpholine, pyrrolidine, and piperidine; teriary amines such as triethylamine, triethanolamine, N,N-dimethylaniline, N-ethylpiperidine, and N-methylmorpholine; hydroxides such as sodium hydroxide; alkoxides such as sodium ethoxide and potassium methoxide; hydrides such as calcium hydride and sodium hydride; and carbonates such as potassium carbonate and sodium carbonate. Preferred salts are those of sodium, potassium, ammonium, ethanolamine, diethanolamine, and triethanolamine. Particularly preferred are sodium salts, for example, the sodium salt of tenidap.

Analytical Methods

The present invention relates to methods of treating hair loss by administering a compound having a structure as described herein. Compounds (test compounds) may be tested for their ability to treat hair loss using the following method. Alternatively, other methods well-known in the art may be used.

Alopecia Areata Mouse Model:

The compounds used in the methods of the present invention may be tested for ability to treat hair loss according to the mouse model set forth in McElwee et al., "Experimental Induction of Alopecia Areata-Like Hair Loss in C3H/HeJ Mice Using Full-Thickness Skin Grafts", *The Journal of Investigative Dermatology*, Vol. 111, pp. 797 - 803 (1998). To test a compound utilized in the present invention, the mouse model may be modified by once-daily or twice-daily dosing a control group and a test compound group throughout the period of the study. The control group is dosed vehicle while the test compound group is dosed from about 0.0001% to about 10%, preferably from about 0.0001% to about 1%, of the test compound in vehicle. The vehicle may be any cosmetically or pharmaceutically acceptable vehicle, however, acetone and methyl sulfoxide (DMSO) are each (independently) preferred vehicles.

Method of Making

The compounds used in the methods of the present invention are prepared according to procedures which are well-known to those ordinarily skilled in the art. The starting materials used in preparing the compounds are known, made by known methods, or are commercially available as a starting material.

It is recognized that the ordinarily skilled artisan in the art of organic chemistry can readily carry out standard manipulations of organic compounds without further direction. Examples of such manipulations are discussed in standard texts such as J. March, Advanced Organic Chemistry, John Wiley & Sons (1992).

The ordinarily skilled artisan will readily appreciate that certain reactions are best carried out when other functionalities are masked or protected in the compound, thus increasing the yield of the reaction and / or avoiding any undesirable side reactions. Often, the artisan utilizes

protecting groups to accomplish such increased yields or to avoid the undesired reactions. These reactions are found in the literature and are also well within the scope of the skilled artisan. Examples of many such manipulations can be found in, for example, T. Greene, Protecting Groups in Organic Synthesis, John Wiley & Sons (1981).

The compounds of the present invention may have one or more chiral centers. As a result, one may selectively prepare one optical isomer, including diastereomers and enantiomers, over another, for example by chiral starting materials, catalysts or solvents, or may prepare both stereoisomers or both optical isomers, including diastereomers and enantiomers at once (a racemic mixture). Since the compounds of the invention may exist as racemic mixtures, mixtures of optical isomers, including diastereomers and enantiomers, may be separated using known methods, such as through the use of, for example, chiral salts and chiral chromatography.

In addition, it is recognized that one optical isomer, including a diastereomer and enantiomer, or a stereoisomer, may have favorable properties over the other. Thus, when disclosing and claiming the invention, when one racemic mixture is disclosed, it is clearly contemplated that both optical isomers, including diastereomers and enantiomers, or stereoisomers substantially free of the other are disclosed and claimed as well.

The syntheses of the compounds useful in the present invention are described in the art. Accordingly, the ordinarily skilled artisan will be able to prepare the compounds described herein. For further guidance, the syntheses of various of the present compounds are described in, for example, Kadin, U.S. Patent No. 4,556,672, assigned to Pfizer Inc., issued December 3, 1985; Reiter et al., WO 90/04393, published May 3, 1990; Schulte et al., U.S. Patent No. 5,059,693 ("Process for Making 3-Aroyl-2-Oxindole-1-Carboxamides"), assigned to Pfizer et al., issued October 22, 1991; Allen et al., EP 277,738, assigned to Pfizer Inc., issued March 18, 1992; Loose et al., U.S. Patent No. 5,545,656, assigned to Pfizer Inc., issued August 13, 1996; Blasko et al., WO 97/36895 ("Process for the Preparation of Tenidap"), published October 9, 1997; Ahmed, WO 97/22605, assigned to Pfizer Inc., published June 26, 1997; and Ahmed, EP 0,826,685, assigned to Pfizer Inc., published March 4, 1998; all of which are herein incorporated by reference in their entirety.

The following non-limiting examples provide even further guidance of making the compounds used in the present method.

Example 1

a) 1-phenoxycarbonyl-2-phenoxycarbonyloxy-5-chloro-indole: A mixture of 5-chloro-oxindole (16.7 g, 0.10 mol), triethylamine (22.2 g, 0.22 mol), phenylchloroformate (34.4 g, 0.22 mol), and tetrahydrofuran (360 mL) is stirred at 20 °C for about one hour. The solvent is removed *in vacuo*, the residue is poured into water, and the precipitate is filtered and collected.

b) 1-phenoxycarbonyl-5-chloro-2-oxindole: 1-phenoxycarbonyl-2-phenoxycarbonyloxy-5-chloro-indole (40.78 g, 0.1 mol) is dissolved in dimethylformamide (200 mL). Ammonium carbonate (7.8 g, 0.08 mol) is added to the solution at around 5 °C. The reaction mixture is stirred until no starting material is detected (about 5 - 8 hours). The reaction mixture is poured on a five-fold volume of water. The precipitated product is filtered, collected, washed with ethanol, and dried.

c) 5-chloro-3-(2-thenoyl)-2-oxindole-1-carboxamide: A mixture of 1-phenoxycarbonyl-5-chloro-2-oxindole (39.78 g, 0.1 mol), ammonium carbonate (15.37 g, 0.16 mol), and dimethylformamide (250 mL) is stirred at about 75 °C for 5 hours. The reaction mixture is added to a mixture of water (500 mL) and hydrochloric acid (conc. 37%) (25 mL) with stirring. The crude precipitate is filtered and collected. The crude precipitate is dissolved in hot methanol (635 mL). 2-amino-ethanol (6.35 g) is added and the solution is clarified with activated charcoal and filtered. Hydrochloric acid (conc. 37%) (18.75 mL) is added dropwise to the filtrate at 40 - 50 °C. The suspension is stirred at 20 - 30 °C for two hours and dried to provide the desired compound.

Example 2

Tenidap Calcium Salt Dihydrate: Tenidap (64.15 g, 200 mmol) is combined with 98% calcium hydroxide (7.94 g, 105 mmol) in dimethylacetamide (160 mL). The resulting mixture is heated to 65 °C for 15 minutes. The mixture is cooled to about 25 °C and filtered. Precipitation is accomplished by the addition of a 50/50 (v/v) mixture of *iso*-propanol and water (480 mL). The resulting mixture is granulated at ambient temperature for about one hour. The partially crystalline product is collected by filtration. The product is charged to about 1240 mL of a 9/1 (v/v) mixture of *iso*-propanol and water. The resulting mixture is heated to reflux for one hour. The mixture is cooled to 60 °C and filtered at that temperature. The resulting product is dried *in vacuo* at 45 °C.

Use of the Present Compounds (Methods of Administration)

The methods of the present invention are performed by administering to a mammal (preferably a human) a composition comprising a compound having a structure as described herein and, preferably, a pharmaceutically-acceptable or cosmetically-acceptable carrier.

The compounds herein may be used for the treatment of such conditions as treating hair loss in mammals, including arresting and / or reversing hair loss and promoting hair growth. Such conditions may manifest themselves in, for example, alopecia, including male pattern baldness and female pattern baldness.

As set forth herein, the compositions of the present invention may be administered in a variety of manners including, for example, oral, rectal, topical, nasal, ocular or parenteral administration. Of these, topical and / or oral administration are especially preferred with

topical being most preferred. Preferably, the topical administration is administration to the scalp. Even more preferably, the topical administration is administration to those areas of the mammal's scalp which is exhibiting lack of hair or thin hair (*i.e.*, bald or balding). The amount of the composition and frequency of application may vary widely, depending on the desired effect and / or the mammal's needs. Typically, the composition is applied from 1 to about 70 times per week, more typically from 7 to about 40 times per week, and most typically about 7 to 21 times per week (*i.e.*, about 1 to 3 times per day).

Preferably, in the methods of the present invention, the compounds are formulated into pharmaceutical or cosmetic compositions for use in treatment or prophylaxis of conditions such as the foregoing. Standard pharmaceutical formulation techniques are used, such as those disclosed in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. (1990).

Typically, the compositions comprise a safe and effective amount, usually at least 0.0001% to about 99.9999%, preferably from about 0.001% to about 50%, more preferably from about 0.01% to about 25%, even more preferably from about 0.1% to about 10%, and most preferably from about 0.1% to about 5% of a compound used in the present invention.

Typically, from about 5 mg to about 3000 mg, more preferably from about 5 mg to about 1000 mg, more preferably from about 10 mg to about 100 mg, of a compound having a structure as described herein is administered per day for systemic administration. It is understood that these dosage ranges are by way of example only, and that daily administration can be adjusted depending on various factors. The specific dosage of the compound to be administered, as well as the duration of treatment, and whether the treatment is topical or systemic are interdependent. The dosage and treatment regimen will also depend upon such factors as the specific compound used, the treatment indication, the efficacy of the compound, the personal attributes of the subject (such as, for example, weight, age, sex, and medical condition of the subject), compliance with the treatment regimen, and the presence and severity of any side effects of the treatment.

According to the present invention, the subject compounds are co-administered as a composition with a pharmaceutically-acceptable or cosmetically-acceptable carrier (herein collectively described as "carrier"). The term "carrier", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a mammal. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with a compound of the present invention, and with each other, in a manner such that there is no interaction which would substantially reduce the efficacy of the composition under ordinary use situations. Carriers must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the animal, preferably mammal (most preferably human), being treated. The carrier can itself be inert or it can possess pharmaceutical and / or cosmetic benefits of its own. The carrier may be

present in the composition at a level of from about 0.00001% to about 99.99999%, preferably from about 1% to about 99.999%, more preferably from about 10% to about 99.999%, still more preferably from about 25% to about 99.9%, even more preferably from about 50% to about 99.9%, and most preferably from about 75% to about 99.9%, all by weight of the composition.

The compositions of this invention may be in any of a variety of forms, suitable (for example) for oral, rectal, topical, nasal, ocular or parenteral administration. Of these, topical and / or oral administration are especially preferred with topical being most preferred. Depending upon the particular route of administration desired, a variety of carriers well-known in the art may be used. These include solid or liquid fillers, diluents, hydrotropes, surface-active agents, and encapsulating substances. Optional pharmaceutically-active or cosmetically-active materials may be included which do not substantially interfere with the activity of the compound of the present invention. The amount of carrier employed in conjunction with the compound is sufficient to provide a practical quantity of material for administration per unit dose of the compound. Techniques and compositions for making dosage forms useful in the methods of this invention are described in the following references: Modern Pharmaceutics, Chapters 9 and 10, Banker & Rhodes, eds. (1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms, 2nd Ed., (1976).

Some examples of substances which can serve as carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the TWEENS; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents, stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

The choice of a carrier to be used in conjunction with the subject compound is typically determined by the way the compound is to be administered.

In particular, carriers for systemic administration include sugars, starches, cellulose and its derivatives, malt, gelatin, talc, calcium sulfate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffer solutions, emulsifiers, isotonic saline, and pyrogen-free water. Preferred carriers for parenteral administration include propylene glycol, ethyl oleate, pyrrolidone, ethanol, and sesame oil. Preferably, the carrier, in compositions for parenteral administration, comprises at least about 90% by weight of the total composition.

Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. These oral forms comprise a safe and effective amount,

usually at least 0.001% to about 99.999%, preferably from about 0.01% to about 50%, more preferably from about 0.1% to about 25%, even more preferably from about 0.1% to about 10%, and most preferably from about 0.1% to about 5% of a compound used in the present invention. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules, and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents and flavoring agents.

The carriers suitable for the preparation of unit dosage forms for oral administration are well-known in the art. Tablets typically comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmelose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets. Capsules (including time release and sustained release formulations) typically comprise one or more solid diluents disclosed above. The selection of carrier components depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of the subject invention, and can be readily made by a person skilled in the art.

Orally administered compositions also include liquid solutions, emulsions, suspensions, powders, granules, elixirs, tinctures, syrups, and the like. The carriers suitable for preparation of such compositions are well known in the art. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, AVICEL RC-591, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate. Peroral liquid compositions may also contain one or more components such as sweeteners, flavoring agents and colorants disclosed above.

Such compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject compound is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate,

polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, Eudragit coatings, waxes and shellac.

Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

The compounds of the present invention may also be topically administered. The carrier of the topical composition preferably aids penetration of the present compounds into the skin to reach the environment of the hair follicle. Topical compositions of the present invention may be in any form including, for example, solutions, oils, creams, ointments, gels, lotions, shampoos, leave-on and rinse-out hair conditioners, milks, cleansers, moisturizers, sprays, skin patches, and the like. Such compositions may be administered using standard methods.

Alternatively, the topical compositions may be topically delivered from a variety of delivery devices. For example, the compositions can be incorporated into a medicated cleansing pad. Preferably these pads comprise form about 50% to about 75% of a substrate and from about 25% to about 50% of a liquid composition deliverable from the substrate. Suitable pads are described, for example, in U.S. Patent 4,891,228; Thurman et al.; issued January 2, 1990; and U.S. Patent 4,891,227; Thaman et al.; issued January 2, 1990.

Alternatively, the compositions useful herein can be incorporated into and delivered from a soft-tipped or flexible dispensing device. These devices are useful for the controlled delivery of the compositions to the skin surface and have the advantage that the treatment composition itself never need be directly handled by the user. Non-limiting examples of these devices comprise a fluid container including a mouth, an applicator, means for holding the applicator in the mouth of the container and a normally closed pressure-responsive valve for permitting the flow of fluid from the container to the applicator upon the application of pressure to the valve. The fluid preferably contains from about 0.01% to about 20%, preferably from about 0.1% to about 10%, and most preferably from about 1% to about 5% of an indoline compound as described herein, all by weight of the fluid (composition).

The valve can include a diaphragm formed from an elastically fluid impermeable material with a plurality of non-intersecting acruate slits therein, where each slit has a base which is intersected by at least one other slit, and where each slit is out of intersecting relation with its own base, and wherein there is a means for disposing the valve in the container inside of the applicator. Examples of these applicator devices are described in U.S. Patents 4,693,623 to Schwartzman; issued September 25, 1987; 3,669,323; Harker et al.; issued June 13, 1972; 3,418,055;Schwartzman; issued December 24, 1968; and 3,410,645; Schwartzman; issued

November 12, 1968; all of which are herein incorporated by reference. Examples of applicators useful herein are commercially available from Dab-O-Matic, Mount Vernon, N.Y.

Topical compositions containing the active compound can be admixed with a variety of carrier materials well known in the art, such as, for example, water, alcohols, aloe vera gel, allantoin, glycerine, vitamin A and E oils, mineral oil, propylene glycol, PPG-2 myristyl propionate, and the like.

Other materials suitable for use in topical carriers include, for example, emollients, solvents, humectants, thickeners and powders. Examples of each of these types of materials, which can be used singly or as mixtures of one or more materials, are as follows:

Emollients, such as stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, *iso*-propyl isostearate, stearic acid, *iso*-butyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, dimethylpolysiloxane, di-*n*-butyl sebacate, *iso*-propyl myristate, *iso*-propyl palmitate, *iso*-propyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, and myristyl myristate; propellants, such as propane, butane, *iso*-butane, dimethyl ether, carbon dioxide, and nitrous oxide; solvents, such as ethyl alcohol, methylene chloride, *iso*-propanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethyl sulphoxide, dimethyl formamide, tetrahydrofuran; humectants, such as glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, and gelatin; and powders, such as chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl ammonium smectites, trialkyl aryl ammonium smectites, chemically modified magnesium aluminium silicate, organically modified montmorillonite clay, hydrated aluminium silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, and ethylene glycol monostearate.

The compounds used in the present invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines. A preferred formulation for topical delivery of the present compounds utilizes liposomes such as described in Dowton et al., "Influence of Liposomal Composition on Topical Delivery of Encapsulated Cyclosporin A: I. An *in vitro* Study Using Hairless Mouse Skin", *S.T.P. Pharma Sciences*, Vol. 3, pp. 404 - 407 (1993); Wallach and Philippot, "New Type of Lipid Vesicle: Novasome®", Liposome Technology, Vol. 1, pp. 141 - 156 (1993); Wallach, U.S. Patent No. 4,911,928, assigned to Micro-Pak, Inc., issued March 27, 1990; and Weiner et al., U.S. Patent No. 5,834,014, assigned to The University of Michigan and

Micro-Pak, Inc., issued November 10, 1998 (with respect to Weiner et al., with a compound as described herein administered in lieu of, or in addition to, minoxidil).

The compounds of the present invention may also be administered by iontophoresis. See, e.g., internet site www.unipr.it/arpa/dipfarm/erasmus/erasm14.html; Banga et al., "Hydrogel-based Iontotherapeutic Delivery Devices for Transdermal Delivery of Peptide/Protein Drugs", *Pharm. Res.*, Vol. 10 (5), pp. 697-702 (1993); Ferry, "Theoretical Model of Iontophoresis Utilized in Transdermal Drug Delivery", *Pharmaceutical Acta Helvetiae*, Vol 70, pp. 279-287 (1995); Gangarosa et al., "Modern Iontophoresis for Local Drug Delivery", *Int. J. Pharm*, Vol. 123, pp. 159-171 (1995); Green et al., "Iontophoretic Delivery of a Series of Tripeptides Across the Skin *in vitro*", *Pharm. Res.*, Vol 8, pp. 1121-1127 (1991); Jadoul et al., "Quantification and Localization of Fentanyl and TRH Delivered by Iontophoresis in the Skin", *Int. J. Pharm.*, Vol. 120, pp. 221-8 (1995); O'Brien et al., "An Updated Review of its Antiviral Activity, Pharmacokinetic Properties and Therapeutic Efficacy", *Drugs*, Vol. 37, pp. 233-309 (1989); Parry et al., "Acyclovir Biovailability in Human Skin", *J. Invest. Dermatol.*, Vol. 98 (6), pp. 856-63 (1992); Santi et al., "Drug Reservoir Composition and Transport of Salmon Calcitonin in Transdermal Iontophoresis", *Pharm. Res.*, Vol 14 (1), pp. 63-66 (1997); Santi et al., "Reverse Iontophoresis - Parameters Determining Electroosmotic Flow: I. pH and Ionic Strength", *J. Control. Release*, Vol. 38, pp. 159-165 (1996); Santi et al., "Reverse Iontophoresis - Parameters Determining Electroosmotic Flow: II. Electrode Chamber Formulation", *J. Control. Release*, Vol. 42, pp. 29-36 (1996); Rao et al., "Reverse Iontophoresis: Noninvasive Glucose Monitoring *in vivo* in Humans", *Pharm. Res.*, Vol. 12 (12), pp. 1869-1873 (1995); Thysman et al., "Human Calcitonin Delivery in Rats by Iontophoresis", *J. Pharm. Pharmacol.*, Vol. 46, pp. 725-730 (1994); and Volpato et al., "Iontophoresis Enhances the Transport of Acyclovir through Nude Mouse Skin by Electrorepulsion and Electroosmosis", *Pharm. Res.*, Vol. 12 (11), pp. 1623-1627 (1995).

The methods of the present invention may also further comprise administering a compound as set forth herein and an activity enhancer. In this context, "further comprising administering" means either administering the compound and the activity enhancer separately (*e.g.*, administration of compound followed by activity enhancer or administration of activity enhancer followed by compound) or wherein the compound and the activity enhancer are administered in the same composition. Further contemplated within the invention herein are compositions comprising a compound as set forth herein and an activity enhancer. The activity enhancer can be chosen from a wide variety of molecules which can function in different ways to enhance hair growth effects of a compound of the present invention. Particular classes of activity enhancers include other hair growth stimulants and penetration enhancers.

Additional hair growth stimulants can be chosen from a wide variety of molecules which can function in different ways to enhance the hair growth effects of the compositions and methods of the present invention. These optional other hair growth stimulants, when present, are typically

employed in the compositions herein at a level ranging from about 0.001% to about 15%, preferably from about 0.01% to about 10%, even more preferably from about 0.1% to about 10%, and most preferably from about 0.5% to about 5%, all by weight of the composition.

Vasodilators such as potassium channel agonists including, for example, minoxidil and minoxidil derivatives such as aminexil and such as those described in U.S. Patent 3,382,247, U.S. Patent 5,756,092, issued May 26, 1998, U.S. Patent 5,772,990, issued June 30, 1998, U.S. Patent 5,760,043, issued June 2, 1998, U.S. Patent 328,914, issued July 12, 1994, U.S. Patent 5,466,694, issued November 14, 1995, 5,438,058, issued August 1, 1995, and U.S. Patent 4,973,474, issued November 27, 1990, (all of which are herein incorporated by reference), and cromakalin and diazoxide can be used as an additional hair growth stimulant in the compositions herein. Particularly preferred methods herein comprise administration of a compound as set forth herein above and minoxidil. Similarly, particularly preferred compositions herein comprise a compound as set forth herein above and minoxidil.

One suitable class of additional hair growth stimulant for use herein are antiandrogens. Examples of suitable antiandrogens may include, but are not limited 5-α-reductase inhibitors such as finesteride and those described in U.S. Patent 5,516,779, issued May 14, 1996 (herein incorporated by reference) and in Nane et al., Cancer Research 58, "Effects of Some Novel Inhibitors of C17,20-Lyase and 5α-Reductase *in vitro* and *in vivo* and Their Potential Role in the Treatment of Prostate Cancer," as well as cyproterone acetate, azelaic acid and its derivatives and those compounds described in U.S. Patent 5,480,913, issued January 2, 1996, flutamide, and those described in U.S. Patents 5,411,981, issued May 2, 1995, U.S. Patent5,565,467, issued October 15, 1996 and U.S. Patent 4,910,226, issued March 20, 1990, all of which are herein incorporated by reference.

Another suitable class of optional hair growth stimulants are immunosuppressants or non-immunosuppressants such as 1) cyclosporin and cyclosporin analogs including those described in U.S. Provisional Patent Application No. 60/122,925, Fulmer et al., "Method of Treating Hair Loss Using Non-Immunosuppressive Compounds", filed March 5, 1999, herein incorporated by reference, and 2) FK506 analogs such as those described in U.S. Provisional Patent Application No. 60/102,449, McIver et al., "Heterocyclic 2-Substituted Ketoamides", filed September 30, 1998, U.S. Provisional Patent Application No. 60/102,448, McIver et al., "2-Substituted Ketoamides", filed September 30, 1998, U.S. Provisional Patent Application No. 60/102,539, McIver et al., "2-Substituted Heterocyclic Sulfonamides", filed September 30, 1998, U.S. Provisional Patent Application No. 60/102,458, Tiesman et al., "Method of Treating Hair Loss Using Ketoamides", filed September 30, 1998, U.S. Provisional Patent Application No. 60/102,437, McIver et al., "Method of Treating Hair Loss Using Sulfonamides", filed September 30, 1998, U.S. Provisional Patent Application No. 60/147,279, Degenhardt et al., "Multivalent Sulfonamides", filed August 5, 1999, U.S. Provisional Patent Application No. 60/147,313,

Degenhardt et al., "Multivalent Exocyclic Diketo Compounds", filed August 5, 1999, U.S. Provisional Patent Application No. 60/147,280, Degenhardt et al., "Multivalent Substituted Ketoamides and Amides", filed August 5, 1999, U.S. Provisional Patent Application No. 60/147,278, Degenhardt et al., "Method of Treating Hair Loss Using Multivalent Ketoamides and Amides", filed August 5, 1999, and U.S. Provisional Patent Application No. 60/147,276, Eickhoff et al., "Multivalent Compounds", filed August 5, 1999, all of which are herein incorporated by reference.

Another suitable class of optional hair growth stimulants are antimicrobials such as selenium sulfide, ketoconazole, triclocarbon, triclosan, zinc pyrithione, itraconazole, asiatic acid, hinokitiol, mipirocin and those described in EPA 0,680,745 (herein incorporated by reference), clinacycin hydrochloride, benzoyl peroxide, benzyl peroxide and minocyclin.

Other anti-inflammatories can also be incorporated into the compositions herein as an optional hair growth stimulant. Examples of suitable anti-inflammatories may include glucocorticoids such as hydrocortisone, mometasone furoate and prednisolone, nonsteroidal anti-inflammatories such as those described in U.S. Patent 5,756,092, and benzydamine, salicylic acid, and those compounds described in EPA 0,770,399, published May 2, 1997, WO 94/06434, published March 31, 1994, and FR 2,268,523, published November 21, 1975, all of which are herein incorporated by reference.

Another suitable class of optional hair growth stimulants are thyroid hormones and derivatives and analogs thereof. Examples of suitable thyroid hormones for use herein may include triiodothyrionine. Examples of thyroid hormone analogs which may be suitable for use herein include those described in U.S. Provisional Patent Application No. 60/136,996, Zhang et al., "Method of Treating Hair Loss", filed June 1, 1999, U.S. Provisional Patent Application No. 60/137,024, Zhang et al., "Method of Treating Hair Loss Using Biphenyl Compounds", filed June 1, 1999, U.S. Provisional Patent Application No. 60/137,022, Zhang et al., "Method of Treating Hair Loss Using Carboxyl Derivatives", filed June 1, 1999, U.S. Provisional Patent Application No. 60/137,023, Zhang et al., "Method of Treating Hair Loss Using Sulfonyl Thyromimetic Compounds", filed June 1, 1999, U.S. Provisional Patent Application No. 60/137,052, Youngquist et al., "Biaryl Compounds", filed June 1, 1999, U.S. Provisional Patent Application No. 60/137,063, Youngquist et al., "Sulfur-Bridged Compounds", filed June 1, 1999, and U.S. Provisional Patent Application No. 60/136,958, Youngquist et al., "Substituted Biaryl Ether Compounds", filed June 1, 1999.

Prostaglandin agonists or antagonists can also be used as optional hair growth stimulants in the compositions herein. Examples of suitable prostaglandins agonists or antagonists include latanoprost and those described in WO 98/33497, Johnstone, published August 6, 1998, WO 95/11003, Stjernschantz, published April 27, 1995, JP 97-100091, Ueno and JP 96-134242, Nakamura.

Another class of optional hair growth stimulants for use herein are retinoids. Suitable retinoids may include isotretinoin, acitretin, and tazarotene.

Another class of optional hair growth stimulants for use herein are triterpenes such as, for example, those disclosed in Bradbury et al., U.S. Patent Application Serial No. 09/353,408, "Method for Regulating Hair Growth", filed July 15, 1999 and Bradbury et al., U.S. Patent Application Serial No. 09/353,409, "Compositions Which Contain Triterpenes for Regulating Hair Growth", filed July 15, 1999, each incorporated by reference in their entirety.

Other classes of optional hair growth stimulants for use herein include flavinoids, ascomycin derivatives and analogs, histamine antagonists such as diphenhydramine hydrochloride, other triterpenes such as oleanolic acid and ursolic acid and those described in U.S. Patent 5,529,769, JP 10017431, WO 95/35103, U.S. Patent 5,468,888, JP 09067253, WO 92/09262, JP 62093215, U.S. Patent 5,631,282, U.S. Patent 5,679,705, JP 08193094, saponins such as those described in EP 0,558,509 to Bonte et al., published September 8, 1993 and WO 97/01346 to Bonte et al, published January 16, 1997 (both of which are herein incorporated by reference in their entirety), proteoglycanase or glycosaminoglycanase inhibitors such as those described in U.S. Patents 5,015,470, issued May 14, 1991, U.S. Patent 5,300,284, issued April 5, 1994 and U.S. Patent 5,185,325, issued February 9, 1993 (all of which are herein incorporated in their entirety by reference) estrogen agonists and antagonists, pseudoterins, cytokine and growth factor promotors, analogs or inhibitors such as interleukin-1 inhibitors, interleukin-6 inhibitors, interleukin-10 promotors, and tumor necrosis factor inhibitors, vitamins such as vitamin D analogs and parathyroid hormone antagonists, Vitamin B12 analogs and panthenol, interferon agonists and antagonists, hydroxyacids such as those described in U.S. Patent 5,550,158, benzophenones, and hydantoin anticonvulsants such as phenytoin.

Other additional hair growth stimulants are described in detail in, for example, JP 09-157,139 to Tsuji et al., published June 17, 1997; EP 0277455 A1 to Mirabeau, published August 10, 1988; WO 97/05887 to Cabo Soler et al., published February 20, 1997; WO 92/16186 to Bonte et al., published March 13, 1992; JP 62-93215 to Okazaki et al., published April 28, 1987; U.S. Patent 4,987,150 to Kurono et al., issued January 22, 1991; JP 290811 to Ohba et al., published October 15, 1992; JP 05-286,835 to Tanaka et al., published November 2, 1993, FR 2,723,313 to Greff, published August 2, 1994, U. S. Patent 5,015,470 to Gibson, issued May 14, 1991, U.S. Patent 5,559,092, issued September 24, 1996, U.S. Patent 5,536,751, issued July 16, 1996, U.S. Patent 5,714,515, issued February 3, 1998, EPA 0,319,991, published June 14, 1989, EPA 0,357,630, published October 6, 1988, EPA 0,573,253, published December 8, 1993, JP 61-260010, published November 18, 1986, U.S. Patent 5,772,990, issued June 30, 1998, U.S. Patent 5,053, 410, issued October 1, 1991, and U.S. Patent 4,761,401, issued August 2, 1988, all of which are herein incorporated by reference.

Non-limiting examples of penetration enhancers which may be used in the compositions herein include, for example, 2-methyl propan-2-ol, propan-2-ol, ethyl-2-hydroxypropanoate, hexan-2,5-diol, POE(2) ethyl ether, di(2-hydroxypropyl) ether, pentan-2,4-diol, acetone, POE(2) methyl ether, 2-hydroxypropionic acid, 2-hydroxyoctanoic acid, propan-1-ol, 1,4-dioxane, tetrahydrofuran, butan-1,4-diol, propylene glycol dipelargonate, polyoxypropylene 15 stearyl ether, octyl alcohol, POE ester of oleyl alcohol, oleyl alcohol, lauryl alcohol, dioctyl adipate, dicapryl adipate, di-isopropyl adipate, di-isopropyl sebacate, dibutyl sebacate, diethyl sebacate, dimethyl sebacate, dioctyl sebacate, dibutyl suberate, dioctyl azelate, dibenzyl sebacate, dibutyl phthalate, dibutyl azelate, ethyl myristate, dimethyl azelate, butyl myristate, dibutyl succinate, didecyl phthalate, decyl oleate, ethyl caproate, ethyl salicylate, *iso*-propyl palmitate, ethyl laurate, 2-ethyl-hexyl pelargonate, *iso*-propyl isostearate, butyl laurate, benzyl benzoate, butyl benzoate, hexyl laurate, ethyl caprate, ethyl caprylate, butyl stearate, benzyl salicylate, 2-hydroxypropanoic acid, 2-hyroxyoctanoic acid, dimethyl sulphoxide, N,N-dimethyl acetamide, N,N-dimethyl formamide, 2-pyrrolidone, 1-methyl-2-pyrrolidone, 5-methyl-2-pyrrolidone, 1,5-dimethyl-2-pyrrolidone, 1-ethyl-2-pyrrolidone, phosphine oxides, sugar esters, tetrahydrofurfural alcohol, urea, diethyl-*m*-toluamide, and, 1-dodecylazacycloheptan-2-one.

In all of the foregoing, of course, the compounds used in the present method can be administered alone or as mixtures, and the compositions may further include additional drugs or excipients as appropriate for the indication.

The present invention further relates to kits comprising a compound and / or composition herein and information and / or instructions by words, pictures, and / or the like, that use of the kit will provide treatment for hair loss in mammals (particularly humans) including, for example, arresting and / or reversing hair loss and / or promoting hair growth. In addition or in the alternative, the kit may comprise a compound and / or composition herein and information and / or instructions regarding methods of application of the compound and / or composition, preferably with the benefit of treating hair loss in mammals.

Examples of Composition Administration

The following examples do not limit the invention, but provide guidance to the skilled artisan to perform the methods of the present invention. In each example, a compound other than the one mentioned may be substituted in the example by another having a structure as described herein with similar results.

Example A

A composition for topical administration is made, comprising:

Component	Amount
Tenidap	5 %
Ethanol	57 %
Propylene Glycol	19 %
Dimethyl Isosorbide	19 %

A human male subject suffering from male pattern baldness is treated by a method of this invention. Specifically, for 6 weeks, the above composition is daily administered topically to the subject.

Example B

A composition for topical administration is made according to the method of Dowton et al., "Influence of Liposomal Composition on Topical Delivery of Encapsulated Cyclosporin A: I. An *in vitro* Study Using Hairless Mouse Skin", S.T.P. Pharma Sciences, Vol. 3, pp. 404 - 407 (1993), using tenidap in lieu of cyclosporin A and using the Novasome 1 for the non-ionic liposomal formulation.

A human male subject suffering from male pattern baldness is treated each day with the above composition. Specifically, for 6 weeks, the above composition is administered topically to the subject.

Example C

A shampoo is made, comprising:

Component	Ex. C-1	Ex. C-2	Ex. C-3	Ex. C-4
Ammonium Lauryl Sulfate	11.5 %	11.5 %	9.5 %	7.5 %
Ammonium Laureth Sulfate	4 %	3 %	2 %	2 %
Cocamide MEA	2 %	2 %	2 %	2 %
Ethylene Glycol Distearate	2 %	2 %	2 %	2 %
Cetyl Alcohol	2 %	2 %	2 %	2 %
Stearyl Alcohol	1.2 %	1.2 %	1.2 %	1.2 %
Glycerin	1 %	1 %	1 %	1 %
Polyquaternium 10	0.5 %	0.25 %	-	-
Polyquaternium 24	-	-	0.5 %	0.25 %
Sodium Chloride	0.1 %	0.1 %	0.1 %	0.1 %
Sucrose Polyesters of Cottonate Fatty Acid	3 %	3 %	-	-
Sucrose Polyesters of Behenate Fatty Acid	2 %	3 %	-	-
Polydimethyl Siloxane	-	-	3 %	2 %
Cocaminopropyl Betaine	-	1 %	3 %	3 %
Lauryl Dimethyl Amine Oxide	1.5 %	1.5 %	1.5 %	1.5 %

Decyl Polyglucose	-	-	1 %	1 %
DMDM Hydantoin	0.15 %	0.15 %	0.15 %	0.15 %
Tenidap	-	5 %	-	-
Tenidap, Sodium Salt	-	-	3 %	-
Pro-form of Tenidap	-	-	-	6 %
Phenoxyethanol	0.5 %	0.5 %	0.5 %	0.5 %
Fragrance	0.5 %	0.5 %	0.5 %	0.5 %
Water	q.s.	q.s.	q.s.	q.s.

A human male subject suffering from male pattern baldness is treated by a method of this invention. Specifically, for 12 weeks, the above shampoo is used daily by the subject.